(54) Title: SYSTEM AND METHOD FOR HEATING THE PROSTATE GLAND TO TREAT AND PREVENT THE GROWTH AND SPREAD OF PROSTATE TUMORS

(57) Abstract: A system and method for safely heating cancerous and pre-cancerous conditions of the prostate, as well as benign and pre-benign lesions (any localized pathological change in the prostate tissue) by irradiation of the prostate tissue with coherent phased array or non-coherent energy is introduced. Microwave energy and prostate compression provide preferential heating of high-water content prostate carcinoma and benign cells in the prostate compared to the surrounding lower-water content normal prostate tissues and tissue surrounding the prostate. To coherently focus the energy, such as microwave energy, in the prostate, the patient's prostate can be compressed via a urethral and rectal balloon and either a single electric-field probe, inserted in the central portion of the prostate, or two noninvasive electric-field sensors on the urethral and rectal walls, can be used to measure a feedback signal to adjust the energy phase delivered to the applicators located in the urethra and in the rectum. The initial energy power delivered to the energy applicators is set to a desired value that is known to produce a desired increase in temperature in the prostate. Temperature feedback sensors are used to measure urethral and rectal wall temperatures during treatment to adjust the energy power delivered to the applicators to avoid overheating the urethral and rectal walls. The energy delivered to the applicators is monitored in real time during treatment, and the treatment is completed when a desired total energy dose has been administered. The system according to the invention can heat and destroy the prostate carcinoma and benign cells sufficiently in order to prevent prostate cancer and benign prostatic hyperplasia. The treatment is administered as a preventative for cancer and BPH, when a patient's PSA level is less than 4 and for BPH, when a patient's AUA Symptom Index scores less than 13.

SYSTEM AND METHOD FOR HEATING THE PROSTATE GLAND TO TREAT AND PREVENT THE GROWTH AND SPREAD OF PROSTATE TUMORS

5   **Background of the Invention**

1. Field of the Invention

The present invention generally relates to a system for administering focused energy to a body selectively using either a single energy applicator or multiple microwave

10   applicators in order to treat visable tumors and microscopic malignant and benign cells in prostate tissue with hyperthermia. The system according to the invention may be used to treat healthy tissue containing undetected microscopic pathologically altered cells (neoplasia) that are of high-water content to prevent the occurrence of or the recurrence of cancerous, pre-cancerous or benign prostatic lesions. In addition, the disclosed system and method for using

15   the system can prevent the growth of tumors inside the prostate, as well as prevent the spread of cancer cells outside the prostate.

2. Description of the Prior Art

In order to treat prostate tumors with hyperthermia, it is necessary to heat a significant portion of the prostate gland while sparing healthy tissues in the prostate as well as the

20   surrounding tissues including the urethral and rectal walls of a patient. In the United States there are approximately 200,000 cases of detected prostate cancer annually as well as 375,000 cases of benign prostatic hyperplasia, known as BPH, (enlarged prostate gland). BPH is a non-cancerous enlargement (tumor) of the prostate gland that occurs in almost all men as they age, particularly past the age of 50 years. In the case of BPH, the enlargement of the prostate

25   involves the excessive growth of tissue that eventually obstructs the bladder outlet, creating difficulties with urination. In the case of prostate cancer, eventually the cancer will break through the prostate gland capsule leading to the spread of cancer to the bones and vital

organs of the body. Although some of the signs of BPH and prostate cancer are the same, having BPH does not increase the chances of getting prostate cancer. Nevertheless, a patient who has BPH may have undetected prostate cancer at the same time or may develop prostate cancer in the future.

5   As is known in the art, the use of heat to treat prostate tumors can be effective in a number of ways; however, in most cases, the heat treatment must be capable of heating a significant volume of the prostate gland without overheating the urethral and rectal walls. In radiation therapy, the entire prostate and adjacent tissues are irradiated with x-rays to kill all the microscopic cancer cells. While heating large volumes of the prostate can destroy many

10   or all of the microscopic carcinoma cells in the prostate, known methods of heating tumors can destroy healthy tissue in the prostate and, more damaging, in the urethral and rectal walls of a patient.

The prostate gland has electrical properties similar to muscle (T.S. England and N.A. .Sharples, Nature, Vol. 163, March 26, 1949, pp. 487-488.) and is known to have a high-water

15   content, on the order of 80% (F.A. Duck, Physical Properties of Tissue, A Comprehensive Reference Book, Academic Press, New York, p. 321, 1990). Tumor tissue, in general, tends to be 10 to 20% higher in water content than normal tissue (Foster and Schepps, Journal of Microwave Power, vol. 16, number 2, pp. 107-119, 1991). Thus, prostate tumors may have a water content on the order of about 90%. Accordingly, selective microwave heating of the

20   prostate would be the best method of targeting cancerous or benign cells.

It is well known that microwave energy can heat high-water content tumor tissues faster when compared to the heating that occurs in lower-water content normal tissues. Tumor tissue tends to be poorly perfused so blood flow often decreases at therapeutic temperatures allowing rapid heating, while in normal tissues the blood flow often increases

protecting the normal healthy tissue from heat damage. Many clinical studies have

established that hyperthermia (elevated temperature) induced by electromagnetic energy

absorption in the microwave band, significantly enhances the effect of radiation therapy in the

treatment of malignant tumors in the human body (Valdagni, et al., International Journal of

5   Radiation Oncology Biology Physics, Vol. 28, pp. 163-169, 1993; Overgaard et al.,

International Journal of Hyperthermia, Vol. 12, No. 1, pp. 3-20, 1996; Vernon et al.,

International Journal of Radiation Oncology Biology Physics, Vol. 35, pp. 731-744, 1996).

Radio-resistant cells such as S-phase cells can be killed directly by elevated temperature

(Hall, Radiobiology for the Radiologist, 4th Edition, JB Lippincott Company, Philadelphia,

10   pp. 262-263, 1994; Perez and Brady, Principles and Practice of Radiation Oncology, Second

Edition, JB Lippincott Company, Philadelphia, pp. 396-397, 1994). Hyperthermia treatments

with microwave radiating devices are usually administered in several treatment sessions, in

which the malignant tumor is heated to about 43° C for about 60 minutes. It is known that

the amount of time to kill tumor cells decreases by a factor of two for each degree increase in

15   temperature above about 43° C (Sapareto, et al., International Journal of Radiation Oncology

Biology Physics, Vol. 10, pp. 787-800, 1984). Thus, a 60-minute heat-alone treatment at 43°

C can be reduced to only about 15 minutes at 45° C, which is often referred to as an

equivalent dose ($t_{43°C}$ equivalent minutes).

During treatments with noninvasive microwave applicators, it has proven difficult to

20   heat semi-deep tumors adequately while preventing surrounding superficial healthy tissues

from incurring pain or damage due to undesired hot spots. The specific absorption rate

(SAR) in tissue is a common parameter used to characterize the heating of tissue. The SAR

is proportional to the rise in temperature over a given time interval times the specific heat of

the tissue, and for microwave energy the SAR is also proportional to the electric field squared times the tissue electrical conductivity. The units of absolute SAR are watts per kilogram.

The first published report describing a non-adaptive phased array for deep tissue hyperthermia was a theoretical study (von Hippel, et al., Massachusetts Institute of

5   Technology, Laboratory for Insulation Research, Technical Report 13, AD-769 843, pp. 16-19, 1973). U.S. Patent No. 3,895,639 to Rodler describes two-channel and four-channel non-adaptive phased array hyperthermia circuits. Likewise, a non-adaptive phased array hyperthermia system was disclosed in U.S. Patent No. 4,589,423 to Turner.

Bassen et al., Radio Science, Vol. 12, No. 6(5), Nov-Dec 1977, pp. 15-25, shows that

10 an electric-field probe can be used to measure the electric-field pattern in tissue, and in particular, shows several examples in which the measured electric-field has a focal peak in the central tissue. This paper also discusses a concept for real-time measurements of the electric field in living specimens. However, Bassen et al. did not develop the concept of measuring an electric field using real-time with an electric-probe to adaptively focus a phased

15 array.

The most difficult aspect of implementing hyperthermia in deep prostatic tissues, with microwave energy, is producing sufficient heating at a predetermined depth while protecting the urethral and rectal walls and surrounding organs from burns. Noninvasive multiple applicator adaptive microwave phased arrays with invasive and noninvasive electric field

20 probes can be used for producing an adaptively focused beam at the tumor position with adaptive nulls formed in healthy tissues as described in U.S. Pat Nos. 5,251,645, 5,441,532, 5,540,737, and 5,810,888 to Fenn, all of which are incorporated herein by reference. Ideally, a focused microwave radiation beam is concentrated at the tumor with minimal energy delivered to surrounding healthy tissue. To control the microwave power during treatment, a

temperature-sensing feedback probe (Samaras et al., Proceedings of the 2nd International

Symposium, Essen, Germany, June 2-4, 1977, Urban & Schwarzenberg, Baltimore, 1978, pp.

131-133) is inserted into the tumor, however, it is often difficult to accurately place the probe

in the tumor. An additional difficulty occurs in delivering hyperthermia to carcinoma spread

5   throughout the prostate gland, because of a lack of a well-defined target position for the

temperature-sensing feedback probe. In other situations, it is desirable simply to avoid

inserting probes (either temperature or E-field) into the prostate tissue in order to reduce the

risk of infection or spreading the cancer cells when the probe passes through the tumor

region.

10   Several articles have been written on the use of dual intracavitary (transurethral and

transrectal) coherent phased array microwave applicators for prostate cancer treatment (A.

Surowiec, et al., Hyperthermic Oncology 1992, Vol. 1, Summary Papers, Proceedings of the

6th International Congress on Hyperthermic Oncology, April 27-May 1, 1992 (Arizona Board

of Regents), p. 268 (abstract); M.M. Yeh, et. al. Hyperthermic Oncology 1992, Vol. 1,

15   Summary Papers, Proceedings of the 6th International Congress on Hyperthermic Oncology,

April 27-May 1, 1992 (Arizona Board of Regents), p. 269 (abstract); and J.C. Camart,

Hyperthermic Oncology 1996, Vol. 2, Proceedings of the 7th International Congress on

Hyperthermic Oncology, Rome, Italy, April 9-13, 1996, pp. 598-600). Further, U.S. Patent

No. 5,007,437 to Sterzer describes the use of non-coherent transurethral and transrectal

20   applicators for BPH treatments. However, the known prior art is directed to the use of

transurethral and transrectal applicators for treating solid tumor masses. None of the known

procedures are concerned with treating microscopic disease and preventing the occurrence of

solid tumor masses such that occur in cancer and BPH.

Prostate Cancer

 The current standard of medical care for treating prostate cancer includes radical or nerve-sparing prostatectomy in which the entire prostate gland is surgically removed, and

5 brachytherapy in which radiation seeds at low dose are permanently implanted in the prostate gland radiating effectively for 6 to 9 months or radiation seeds at high dose are temporarily implanted in the prostate for about 2 days, combined with external-beam radiation therapy to catch microscopic cancer cells that may have penetrated or could penetrate the prostate capsule. Side effects from surgery include incontinence and impotence. The cancer

10 recurrence rate after surgery can be as high as approximately 35% at 5 years, and approximately 60% at 10 years, particularly when the prostatic-specific antigen level (discussed below) is greater than 10. Radiation therapy has short-term side effects such as skin reactions, fatigue and nausea. Additional long-term side effects of radiation therapy to the prostate include urinary incontinence (loss of bladder control) and impotence, as well as

15 damage to surrounding organs.

 Hormone therapy is also used to supplement prostate cancer treatments by stopping cancer cells from growing. Male hormones, such as testosterone, help cancer cells grow and, in contrast, female hormones or estrogens inhibit growth. Side effects of estrogen therapy include nausea and vomiting, hot flashes, fluid retention, weight gain, headaches and

20 gynecomastia (an increase in breast tissue) in men.

 Fundamentally, the problem with current prostate treatments is the inability to control microscopic capsule penetration from the prostate gland, which spreads the cancer to vital organs. Men with microscopic capsule penetration of cancer cells are not cured by radical

prostatectomy. These microscopic cells may spread far from the prostate gland into vital

organs by means of the lymphatic system or by blood vessels through the prostate capsule.

It is possible to detect the presence of prostate cancer by means of the well-known

serum assay Prostate-Specific Antigen (PSA) test (M.K. Brawer, "Prostate-Specific Antigen:

5   Current Status," CA A Cancer Journal for Clinicians, Vol. 49, pp. 264-281, 1999, and J.E.

Oesterling, "Prostate Specific Antigen: A Critical Assessment of the Most Useful Tumor

Marker for Adenocarcinoma of the Prostate," The Journal of Urology, Vol. 145, pp. 907-923,

May 1991.). The prostatic lumen contains the highest concentration of PSA in the human

body. PSA is an enzyme produced in all types of prostatic tissue (normal, benign

10   hyperplastic and malignant). In particular, PSA is a serine protease that is produced only by

the epithelial cells lining the acini and ducts of the prostate gland; none of the other cellular

components of the prostate, including the stromal and vascular elements produce PSA.

Researchers have verified that PSA is produced in the epithelial cells of BPH tissue, primary

prostate cancer tissue, and metastatic prostate cancer tissue. The serum PSA test detects a

15   significant number of prostate cancers and the destruction of prostatic tumors leads to

reduced PSA levels, since the body stops producing PSA when the tumors are eliminated.

Currently, a PSA level of 4.0 ng/ml or greater is used to decide whether a patient will be

biopsied to try to verify the presence of carcinoma in the prostate. Thus, patients with a PSA

level under 4.0 ng/ml currently are not biopsied even if they experience the signs and

20   symptoms of prostate cancer which may include: frequent urination, especially at night,

inability to urinate, trouble starting or holding back urination, a weak or interrupted urine

flow and frequent pain or stiffness in the lower back, hips or upper thighs.

In addition to PSA level, the Gleason Grade is used to histologically grade adenocarcinoma of the prostate (G.K. Zagars, et al, International Journal of Radiation Oncology Biology Physics, Vol. 31, No. 2, pp. 237-245, 1995), with Grade 1 being the least malignant and slowest growing. Gleason Grade 3 is the most commonly occurring grade when diagnosed. Gleason Grades 4, 5 and above (up to 10) are considered highly aggressive, rapidly growing carcinomas.

Biopsy results and staging are used to predict the behavior of the cancer and the likelihood of its spread. Stage 1 tumors are small and cannot be felt on rectal examination. Stage 2 or greater refers to prostates in which the tumor can be felt. Stage 3 cancers have spread beyond the boarders of the prostate. In Stage 4, which can be determined by imaging studies such as bone scans, CT, or MRI scans, the cancer has spread into nearby lymph glands, the bones, or elsewhere in the body. As is well known in the medical field, the earlier the cancer is detected, the better the chance of being a cancer survivor. If detection is not possible before stage 2, the next best medical option would be to safely treat apparently healthy tissue. Thus, there is a need to treat healthy tissue since cancer, in general, cannot be detected until it has reached stage 2 or a later stage.

There are four types of prostate ductal carcinomas: transitional cell carcinoma, intraductal adenocarcinoma, mixed ductal carcinoma, and endometrioid carcinoma. Transitional cell and mixed ductal carcinomas are aggressive cancers that require complete removal of the prostate and bladder if found while the tumor is still confined to the prostate. Complete removal of the prostate and bladder is also the medically accepted treatment for endometrioid carcinoma. Intraductal adenocarcinomas are treated by radical prostatectomy. Thus, there is a need for a system for treating and preventing the growth and spread of cancer that does not require surgical prostatectomy.

Benign Prostatic Hyperplasia

Benign Prostatic Hyperplasia (BPH) is described primarily as an enlargement of the

prostate gland that exerts pressure on the urethra, resulting in obstruction of the flow of urine,

and is a common affliction in middle-aged and older males. Approximately 50% of men

5   older than 65 years will have BPH symptoms that significantly affect their quality of life. The

American Urological Association (AUA) Symptom Index was developed to help categorize

BPH symptoms. The AUA score has the following score ranges: 0 to 7 points – BPH

symptoms are considered mild; 8 to 19 points – BPH symptoms are considered moderate;

and 20 to 35 points - BPH symptoms are considered severe. However, many BPH patients

10   do not seek treatment until their AUA score is about 12.

Over the last two decades, a number of treatments for BPH have been developed each

with advantages and disadvantages. The major types of BPH treatment systems are: 1)

transurethral resection of the prostate (TURP), 2) Transurethral Electrovaporization of the

Prostate (TVP), 3) Drugs, 4) Interstitial Laser Coagulation, 5) RF Needle Ablation, and 6)

15   Microwave Thermotherapy of the Prostate. Other treatment techniques have been explored,

including transurethral incision of the prostate, prostatic stents, and balloon dilation, but are

used to a lesser extent.

BPH treatment success and practicality can measured in terms of 1) efficacy, 2)

durability, 3) level of pain (during and after the procedure), 4) recovery period, 5) complexity

20   of the procedure, 6) cost of the procedure, and 7) side effects. Efficacy of BPH treatments is

commonly quantified using the AUA Symptom Index (SI) and peak urine flow rate. Normal

urine flow rate is about 16 ml/sec. Other optional tests such as residual urine volume and

pressure flow are sometimes used to judge efficacy. Durability is the length of time for which

the treatment is effective. The level of pain relates primarily to the need for either general

anesthesia or local anesthesia. The recovery period is measured in terms of the number of

days of hospitalization and home rest. The complexity of the procedure is a function of the

length of the procedure, the training of the individual administering the procedure (either an

urologist or a technician), the type of anesthesia required, and the length of time needed for

5   Foley catheterization after treatment. The cost of the procedure is influenced strongly by the

length and complexity of the procedure - particularly whether a hospital stay is required.

Until about 1990, the major treatment ("Gold Standard") for BPH was Transurethral

Resection of the Prostate (TURP) which is administered by urologists. TURP is expensive,

requires a long recovery time, and has a number of significant side effects, which has

10   prompted the search for better treatment techniques. A summary of approaches to treat BPH,

including surgery, drug and laser, RF, and microwave applications is described below.

Transurethral Resection of the Prostate (TURP):

The "Gold Standard" of BPH treatments involves a surgical procedure in which a

rigid transurethral scope with an electrosurgical loop is used to remove part of the enlarged

15   prostate tissue (primarily the central zone of the prostate) with RF energy. In practice, 90%

of surgical procedures for BPH involve TURP, due to its excellent efficacy (85% or more),

long-term durability (10 to 15 years) for 90% of patients. On the order of 200,000 TURPs are

performed in the United States annually. TURP has a number of drawbacks: It is a very

painful procedure and requires both 2-4 days of hospitalization and 2-4 weeks of recovery at

20   home. The TURP procedure is performed in about one hour and requires general anesthesia.

An urologist must perform the procedure. A Foley catheter is required for about 2-3 days

post treatment. Some of the major potential side effects of a TURP include impotence,

incontinence, high blood loss, and retrograde ejaculation.

Open Prostatectomy:

An open prostatectomy is primarily used on patients with very large prostates with

excellent results: the efficacy is greater than 95% and the durability is the same as TURP (10

to 15 years). With any surgical procedure, the pain level is very high and general anesthesia

5   is required. About 7 to 10 days of hospitalization is required with an additional 3-5 weeks

spent at home. The procedure takes a few hours and must be performed by a urologist.

Following the treatment, a Foley catheter must be used for 2-4 days to drain the bladder. An

open prostatectomy is about twice the cost of a TURP, and has the serious potential side

effects and complications including high blood loss, impotence, and incontinence.

10   Transurethral Electrovaporization of the Prostate (TVP):

Basically a modification of TURP, transurethral electrovaporization of the prostate

employs a grooved electrosurgical rollerball electrode to channel open the urethra that is

blocked by the prostate tissue. The TVP procedure is safer and has minimal side effects

compared to TURP. The efficacy is excellent (85%), but still is a very painful procedure

15   requiring 2-4 days of hospitalization and 1-2 weeks at home. A urologist performs this 60-

minute procedure and the patient is under a general anesthetic. A Foley catheter must be used

for 2-4 days following this procedure. The procedure costs slightly less than TURP. There is

less blood loss than with TURP, but their are still the potential side effects of impotence,

incontinence, and retrograde ejaculation.

20   Transurethral Incision of the Prostate (TUIP):

In a relatively new procedure for patients with small prostates, transurethral incision

of the prostate provides an efficacy of about 80%. However, TUIP is not effective on large

prostates. A minimal amount of prostate tissue is removed in this procedure - a simple

incision is made along the entire length of the prostate. The TUIP procedure allows the

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bladder neck to spring open, allowing free urinary flow. The durability is expected to be

similar to TURP, but clinical research is still in progress. This procedure is moderately

painful and requires only a day or two of hospitalization, or for some patients is an outpatient

procedure. Usually, 4 to 7 days of home rest are needed following the procedure. A urologist

5   must perform this 60-minute surgical procedure and a Foley catheter must be used for 2 to 4

days. The cost of the TUIP is about the same as TURP. There is less blood loss with this

procedure compared to TURP, but there are still the potential side effects of impotence,

incontinence, and retrograde ejaculation.

Balloon Dilation:

10   For patients with small prostates, balloon dilation within the prostatic urethra can be

used to offer some relief from BPH symptoms. The efficacy is only about 60% and the

durability is only 1 to 5 years. This procedure is less costly than TURP and is usually

performed as an outpatient with several days of home rest. The procedure is performed under

local anesthesia by a urologist in about 30 minutes. A Foley catheter is required for about 2-4

15   days. There may be some bleeding in this procedure and there are the possible side effects of

infection and impotence. The procedure does not work well on large prostates.

Stents:

For very ill patients with small prostates, stents can be used with good effectiveness to

improve BPH symptoms. Durability is not a major issue since these patients are usually very

20   ill with other diseases. This procedure is moderately painful and requires only local

anesthesia, is performed in about 30-minutes by a urologist, and is done as an outpatient with

about 4-5 days of home rest. The cost of this procedure is less costly than TURP. Some of

the potential side effects are irritation, infection, and the formation of debris on the stent.

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Drugs:

Two categories of drugs are used in treating BPH. One category uses an alpha blocker (Hytrin or Cardura) to relax the muscles that surround the prostate to allow better urinary flow. The other type of drug is reductase inhibitor (Proscar) which actually shrinks the

5   prostate gland.

Hytrin, for example, has very good efficacy (74%) and offers some immediate relief of BPH symptoms, however 2-3 weeks are needed until the full effectiveness is reached. Clinical data suggests that this drug has at least 3 to 5 years durability and is simply prescribed by a general practitioner. The cost is less than TURP depending on the number of

10   years of treatment. There can be some serious side effects such as dizziness, chest pain, irregular heartbeat, and shortness of breath.

Proscar works well on large prostates, but is ineffective on small prostates. Full effectiveness of the drug takes about 3 to 6 months and the durability is estimated at least 3 to 5 years. This drug is prescribed by a general practitioner and must be taken for at least 12

15   months. The cost of the drug is less than TURP. Some of the known side effects are impotence, swollen lips, decreased volume of ejaculate, and skin rash.

Interstitial Laser Coagulation:

Here, an interstitial laser coagulation surgical device delivers laser energy radially along the length of a custom-designed light diffuser. The diffuser produces an ellipsoidal

20   pattern of thermal damage, applying the laser energy omnidirectionally and uniformly, to maximize treated tissue volume in the prostate. This is a moderately painful surgical procedure, requiring one or two days in the hospital and then 1 to 2 weeks at home. This 30-minute procedure must be performed by a urologist, with a choice of either general or local anesthesia depending on the patient's condition. A serious disadvantage with this procedure

is the lengthy required time of 1 to 2 weeks in which a Foley catheter must be used to drain

the bladder of urine. The cost of the procedure is less than TURP. There are many potential

side effects from this treatment including impotence, incontinence, blood loss, and retrograde

ejaculation.

5   RF Needle Ablation (Transurethral Needle Ablation):

This system uses two high-energy RF (approximately 0.47 MHz) needles that are

inserted through the urethra into the prostate, to ablate the prostate tissue in a few minutes.

More than 10,000 patients worldwide have been treated with this system, which provides

good to very good efficacy. There is only limited 12-month durability data for this system, so

10   the long-term effectiveness is not known. The procedure is moderately painful (local

anesthesia required) and is performed as an outpatient with 1-2 weeks for home recovery.

The procedure is usually performed by a urologist in about 30 minutes. About 40% of

patients will require a Foley catheter for about 2 to 3 days. The procedure costs less than

TURP. The major side effects from this procedure are irritating voiding, erectile dysfunction,

15   and retrograde ejaculation.

In view of the known treatments for BPH, which require costly, painful, surgery or

drugs which have potentially dangerous side effects, there is a need for a system of treating

benign prostatic hyperplasia (BPH) that is not painful; can be accomplished on an outpatient

basis; and quickly restores the patient to his normal functions. In addition, a method is needed

20   that can safely treat the prostrate gland with focussed energy before a significant amount of

microscopic tumor cells form in the prostate.

Summary of the Invention

The above problems associated with known treatments are solved by the system and

method for using the system according to the invention. The system and method according to

the invention safely heat pre-cancerous, cancerous, pre-benign, and benign conditions of the

prostate by heating the prostate gland with focussed or concentrated energy, such as

microwave energy, delivered by either phase non-coherent or coherent array applicators in the

urethra and rectum, or with interstitial applicators positioned within the prostate. In a non-

5   coherent array, separate microwave oscillators can drive the applicators and there is no

common phase relation. In a phase coherent array (phased array), a single microwave

oscillator can drive multiple applicators with a common phase relation.

The Applicants' approach is to treat the prostate gland with focussed energy, such as

microwave energy before a significant amount of microscopic tumor cells form in the

10   prostate gland. As described above, all past uses of thermal therapy were used for the

treatment of established prostate cancers with moderate to high PSA levels (over 4.0 ng/ml)

or for the treatment of moderate to severe AUA symptom index scores for BPH. The

preferred embodiment of this invention is for the prevention or before detection, or before

medical intervention is required. Thus, the inventive method is for treating prostate cancer

15   when the PSA level is less than 4.0 ng/ml, or for treating BPH where BPH symptoms are less

than severe or the AUA symptom index score is less than 13. In other words, the inventive

method is to prevent the cancer or BPH from developing into a significant problem for a

patient (i.e., before serious adverse effects occur).

The preferred method of treating a prostate, according to the invention, is with a

20   coherent adaptive phased array and comprises the steps of monitoring temperatures of walls

of the urethra and rectum, orienting two microwave applicators in at least one of the urethra

and rectum, adjusting the microwave power to be delivered to the prostate based on the

monitored urethral and rectal wall temperatures, monitoring the microwave energy dose

delivered to the prostate being treated and automatically completing the treatment when a

desired total microwave energy dose has been delivered by the microwave applicators.

Incoherent-array or non-adaptive phased array hyperthermia treatment systems can be

used to heat semi-deep and deep tissue, depending on the radiating frequency. Due to the

5   dielectric heating of high-water content tissue such as prostate tumor, it may be possible to

safely heat prostate tumors with either non-coherent arrays or non-adaptive phased arrays.

Moreover, the system and method according to the invention have application in

situations where there is no well-defined position to place the temperature feedback sensor, or

where it is desirable to avoid inserting a temperature probe into the prostate tissue. In the

10   case of a single applicator, an E-field probe (or E- field sensors) is not necessary and thus, an

invasive probe is not required in the preferred system and method according to the invention.

The inventive system and method may destroy all of the prostate pre-cancerous and

cancerous cells or benign lesions with heat generated by the focussed energy thereby avoiding

further progression of the cancer cells or benign lesions.

15   In addition, the method according to the invention can be used to enhance radiation

therapy or for targeted drug delivery and/or targeted gene therapy delivery with or without

thermosensitive liposomes as described in U.S. Pat. No. 5,810,888 to Fenn.

The method according to the invention destroys the pre-cancerous, cancerous, pre-

benign, and benign cells in the prostate while preserving normal prostate tissue. Thus, the

20   system and method according to the invention achieves a thermal prostatectomy and avoids

damage to healthy tissue. Accordingly, the inventive method is a prostate conservation

technique.

The urethral and rectal wall temperature can be measured by temperature probe

sensors positioned away from the transurethral and transrectal applicators to obtain the true

temperature of the urethral and rectal walls. Alternatively, the tissue temperatures can be

monitored by external means, including infrared, laser, ultrasound, electrical impedance

tomography, magnetic resonance imaging, and radiometry techniques as known in the art.

Alternatively, a temperature probe could be inserted at an appropriate depth in the

5   prostate tissue to monitor the temperature thereof. As discussed below, insertion of a

temperature probe is not a preferred embodiment.

In an embodiment with two or more energy applicators, an invasive E-field probe,

inserted in the prostate, may or may not be used to measure the microwave power delivered to

the tissue to be treated to determine the length of the focussed energy treatment. In a

10   preferred embodiment, the invasive E-field probe can be used to focus the applied energy at

the E-field probe inserted in the prostate.

As an alternate embodiment, for a coherent phased array, two E-field sensors can be

placed in the prostatic urethra and rectum non-invasively and be used to null the E-field in the

urethra and rectum and effectively focus the microwave radiation in the prostate tissue.

15   Additionally, the microwave phase for the transurethral and transrectal applicators can be

adjusted so that the microwave energy is scanned across an area of the prostate.

The system and method according to the invention can be achieved with or without

compression of the prostate. In a preferred method, a patient's prostate would be compressed

by expanding at least one of a urethral balloon and a rectal balloon. Focussed energy and

20   prostate compression provide preferential heating of high-water content prostate carcinoma

and benign cells in the prostate compared to the surrounding lower-water content normal

prostate tissues and tissue surrounding the prostate.

To coherently focus the energy, such as microwave energy, in the prostate, the

patient's prostate can be compressed via a urethral and rectal balloon and means for

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determining where to focus the energy in the patient's prostate is used. The means for

determining where to focus the energy can be either a single electric-field probe, inserted in

the central portion of the prostate, or two noninvasive electric-field sensors on the urethral

and rectal walls. The probe or sensors receive signals that can be used to measure a feedback

5   signal in order to adjust the energy phase delivered to the applicators located in the urethra

and in the rectum.

The major advantages offered by treatment according to the system and method of the

invention over known treatments are listed below:

1. Prevention and destruction of prostate tumors (including cancerous and benign);

10   2. Immediate relief from any BPH symptoms that might exist;

3. Long term durability;

4. Only low level pain may be experienced;

5. Outpatient procedure;

6. Local anesthesia;

15   7. No Foley catheter required; and

8. No significant side effects or complications.

A biological stent can be formed in the prostatic urethra due to the combination of

compression balloon dilation and microwave heat (microwave urethroplasty) as evidenced in

clinical tests held by the assignee, Celsion Corporation, during 1999. As a result, one of the

20   major deficiencies in known BPH treatments, namely the need for a Foley catheter for several

days, is no longer needed and a patient may experience immediate relief from BPH

symptoms.

As described below, applicants' inventive system and method involves monitoring the

microwave energy dose delivered to the prostate being treated and completing the treatment

based on the total microwave energy dose that has been received. That is, conventional

temperature feedback measurements of tumor thermal dose can be replaced with the total

microwave energy delivered to the coherent phased array or non-coherent microwave

applicators and then to the treated area. Accordingly, with the instant invention, instead of

5   temperature feedback measurements, which require the insertion of a temperature feedback

probe into the prostate and its inherent problems, microwave energy dose is used as a

feedback to determine the required length of treatment. In this application the term

"microwave energy dose" (in Joules or watt-seconds) is similar to the dose used in radiation

therapy, namely the radiation absorbed dose (Rad) which is a unit of absorbed dose of

10   radiation defined as deposition of 100 ergs of energy per gram of tissue.

       Thus, the instant method for selectively heating cancerous and benign conditions of

the prostate avoids the risk of spreading cancer cells since the temperature probe is not

inserted into the treated area (tumor bed) of the prostate. The elimination of an inserted

temperature probe reduces the risk of infection to a patient as a result of the inserted probe.

15   Likewise, the microwave field applied to a tumor would not be subjected to scattering or

other disturbance caused by a temperature probe, especially a metallic probe. In addition, the

time and costs associated with inserting the temperature probe are saved.

       The inventive system and method may also be used to treat healthy prostate tissue or

undetected high-water content microscopic pre-cancerous or pre-benign cells in seemingly

20   healthy prostate tissue to prevent the occurrence of or recurrence of cancerous conditions of

the prostate. Thus, the system and method according to the invention would be able to

destroy or ablate microscopic precancerous or pre-benign cells in the prostate gland that are

higher in water content (e.g., 90%) than the prostate gland (e.g., 80%) before they are

detected. This would be an early treatment that could prevent cancer from growing in the

prostate and spreading from the prostate, or enlargement of the prostate gland. In the case of seemingly healthy tissue, the prostate tissue would be irradiated with microwave energy focused at high-water content microscopic cells that are known to form lesions without damaging the healthy lower-water content prostate tissue.

5   If both transurethral and transrectal applicators are used and both are expanded by respective balloons, a preferred system having means for compressing and immobilizing the prostate to reduce the tissue penetration depth and to reduce the prostate blood flow is achieved.

In an alternate method, the prostate is compressed with a single transurethral balloon,

10   which immobilizes the prostate tissue, reduces blood flow, and reduces the penetration depth required for the microwave radiation. The compression balloon is made of a microwave transparent plastic material such as Latex. The placement of an E-field feedback probe in the prostate may be achieved with an ultrasound transducer or other type of image guidance. Further reduction in blood flow can be achieved, in a preferred method, by injecting a local

15   anaesthetic lidocaine with ephinephrine or anti-angiogenesis drug in the prostate.

Two microwave applicators (such as described by U.S. Pat. No. 5,007,437 to Sterzer which is incorporated herein by reference) can be positioned transurethrally and transrectally. A phased array can be achieved with a multiple number of applicators greater than or equal to two. In a preferred embodiment, coherent 915 MHz microwave power is delivered to the

20   two transurethral and transrectal applicators, at a predetermined power level, while phase shifters in each channel are adjusted to maximize and focus the microwave energy at the E-field probe sensor. Water-cooling within the catheters and balloons allows cooling of the urethral and rectal walls. Additional interstitial applicators can be inserted within the prostate to supplement the heating that is produced by the transurethral and transrectal applicators.

During the hyperthermia treatment, the microwave power level delivered to each of

the applicators may be adjusted either manually or automatically to avoid high temperatures

that could cause burns or blisters to the urethral or rectal walls. In addition, the amount of

prostate compression, if used, is adjusted as necessary during treatment to provide patient

5   comfort. Each time the prostate compression is adjusted, the microwave-energy/phased array

is refocused so that the E-field probe sensor receives maximum power. The total microwave

energy, since the start of the treatment, delivered to the microwave applicators is monitored

during the treatment. The treatment is completed when a desired amount of total microwave

energy is delivered to the microwave applicators, which indicates that the lesion cells are

10   significantly destroyed (i.e., thermal downsizing) or completely destroyed (i.e., thermal

prostatectomy).

In order to determine the effectiveness of the treatment, the prostate tissue may be

imaged and examined with one of x-ray, ultrasound, and magnetic resonance imaging before

and after the microwave total energy dose is administered, as well as with pathological results

15   from needle biopsy of the prostate tissues.

In an alternate embodiment of the invention, the single invasive E-field probe is

replaced with two E-field sensors positioned in the urethra and rectum and the coherent array

is phase focused by minimizing (nulling) the individual or combined power received by the

two sensors, providing a completely noninvasive treatment. In a preferred embodiment, the

20   two E-field sensors are contained with catheters attached to the outside surface of a

compression balloon which provides a pressure contact to the urethal and rectal walls.

Algorithms are used in conjunction with the feedback signals sensed by the E-field sensors to

null areas on the urethral and rectal walls outside thereby focussing the applied energy on an

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internal site. After the nulling algorithm is completed, the E-field sensors can be withdrawn and temperature sensors can be inserted to measure the urethal and rectal wall temperatures.

Such a totally non-invasive hyperthermia treatment where E-field sensors and temperature sensors monitor the urethral and rectal walls would provide an effective method

5   of destroying benign and cancerous lesions in the prostate. In an embodiment with non-coherent applicators, an E-field focussing probe and phase shifters are not required to heat the tissue. With non-coherent energy, only the applicator radiated power is additive and phase shift is not used.

While the preferred embodiment is described with reference to adaptive microwave

10   phased array technology, Applicants' system and method may be achieved by focussing energy, in general, to heat and ablate an area of tissue. The focused energy may include electromagnetic waves, ultrasound waves or waves at radio frequency. That is, applicants' inventive system and method includes any energy that can be focused to heat and ablate an area of tissue. This energy, such as microwave or ultrasound energy, can be coherent or non-

15   coherent.

In yet another embodiment of the invention with a coherent phased array, the boundary of an area of tissue to be treated in a body (e.g., prostate) is calculated, an E-field probe may be inserted in the body or at least two E-field sensors are positioned within the urethra and rectum; and energy is applied through applicators to the area to be treated. In this

20   embodiment, the focus of the energy would change so that the focus scans the area to be treated. That is, there is no longer a fixed focus spot as the relative phase of the applied energy would be adjusted so that the focus moves inside the area to be treated thereby obtaining a geometric shape of heating.

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A fixed focus spot is determined through the appropriate algorithm. Then, for example, the relative phase of the applicators to obtain this fixed focus spot is adjusted 30° one way and then 30° the other way to "scan" a larger heated/treated area. Depending on the size of the area to be treated the scan may focus between 180° and 90° or 60° or 120°.

5   Further objectives and advantages will become apparent from a consideration of the description and drawings.

Brief Description of the Drawings

The invention is better understood by reading the following detailed description with reference to the accompanying figures, in which like reference numerals refer to like elements

10   throughout, and in which:

Fig. 1 shows the microwave thermotherapy system according to the invention for heating the prostate under compression from coherent transurethral and transrectal applicators; and

Fig. 2 shows the microwave thermotherapy system according to the invention for

15   heating the prostate under compression from non-coherent transurethral and transrectal applicators.

Detailed Description of the Preferred Embodiment

Description of the Prostate Gland and its Microwave Properties

The prostate gland 220 is part of the male reproductive system and is a solid, walnut-

20   shaped organ that surrounds the first part of the urethra 205 immediately under the bladder 202 and in front of the rectum 210. Prostate cancer arises from the glands of the prostate and the most common form of prostate cancer is known as adenocarcinoma, which means a cancer of the glands. Most prostate cancers develop within the bottom portion of the prostate (sometimes referred to as the peripheral zone which involves roughly 70% of the glandular

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prostate) closest to the rectum, and this is the region that needs a significant amount of treatment. While a digital rectal exam is useful in detecting hardened areas or lumps in the prostate gland, however it is not very useful for detecting microscopic prostate disease. The use of a transrectal applicator (in addition to a transurethral applicator) to reach this portion of

5   the prostate is essential for a complete treatment of the prostate. The central zone of the prostate (closest to the bladder) is relatively immune to both BPH and prostate cancer diseases. BPH arises mainly in the transition zone located between the central zone and peripheral zone.

As discussed above, current medical procedure does not biopsy a tumor until a PSA of

10   4.0 ng/ml is reached. The data shown in Table 1 indicate that there is only about a 15% probability of detecting cancer by needle biopsy when the PSA is less than 4 ng/ml. Although the probability of detecting the cancer is very low, the actual probability that there are microscopic cancer cells in the prostate is significant (25% or more) (F.H. Schröder et al, The Journal of Urology, Vol. 163, No. 3, p. 806 (abstract), March 2000) (Eschenbach et al.,

15   CA Cancer J. Clinicians, Vol. 47, pp. 261-264, 1997). Thus, thermotherapy treatment of the prostate

PSA Level	Probability of Detecting Prostate Cancer on Initial Biopsy
2 ng/ml	1%
2-4 ng/ml	15%
4-10 ng/ml	25%
> 10 ng/ml	>50%

Table 1. Probability of detecting cancer on initial biopsy for different levels of PSA.

is likely warranted, even if the PSA level is in the range of 0 to 4 ng/ml. Thermotherapy

treatment of the prostate for PSA levels below 4 ng/ml is intended to kill the microscopic

cancer cells in the prostate and keep the PSA from rising above 4 ng/ml.

Microwave radiation in the Industrial, Scientific, Medical (ISM) band 902 to 928

5   MHz is commonly used in commercial clinical hyperthermia systems, and is the primary

frequency band considered here. It is known that the prostate is high-water content tissue

and, hence, is similar to muscle tissue which is well characterized. For normal prostate tissue

at 915 MHz, the average dielectric constant is 50 and the average conductivity is 1.3 S/m.

The calculated loss due to attenuation of a 915 MHz plane wave propagating through prostate

10   tissue is approximately 3 dB per cm. Prostatic intraepithelial neoplasia, also known as

atypical hyperplasia and intraductal dysplasia are pre-cancers and are associated with the

development of adenocarcinoma of the prostate. The neoplastic cells are assumed to be

higher-water content than the surrounding normal prostate cells and will be heated faster than

the normal healthy prostate cells. The normal ductal tissue in the prostate is assumed to be in

15   the low- to medium-water content range.

The safety of employing radiofrequency (microwave) electromagnetic fields in order

to treat cancer has been questioned. A comprehensive study recently concluded that there is

no association between the incidence or promotion of cancer and exposure to radiofrequency

electromagnetic fields in the frequency range of 3 KHz to 300 GHz (L.N. Heynick,

20   Radiofrequency Electromagnetic Fields (RFEMF) and Cancer: A Comprehensive Review of

the Literature Pertinent to Air Force Operations, AFRL-HE-BR-TR-1999-0145, United States

Air Force Research Laboratory, Directed Energy Bioeffects Division, June 1999). Thus,

based on this report, the Applicants realized that there is significant evidence that microwave

treatment of the prostate can safely heat an apparently healthy prostate gland containing

microscopic cancer cells such that no new cancer would be formed as a result of the microwave treatment.

<u>System for Heating Prostate Tissues</u>

Figure 1 shows a preferred system for heating carcinomas and benign tumor cells in

5   prostate tissues, using an adaptive energy, preferably microwave, phased array hyperthermia system with E-field and temperature feedback. In order to heat deep tissues reliably at energy frequencies, it is necessary to surround the body (prostate lobes **220**) with two or more energy applicators **110, 111** (within the urethra **205** and rectum **210**, respectively) controlled by an adaptive phased array algorithm. The energy applicators **110, 111** may be coherent

10   microwave applicators. The blackened circle, indicated as focus **190**, represents a central tumor or healthy tissue of the prostate **220** that is to be treated.

Focus **190** may represent cancerous conditions of the prostate including one of adenocarcinoma, carcinosarcoma, rhabdomyosarcoma, chondrosarcoma, and osteosarcoma, or pre-cancerous conditions including one of prostatic intraepithelial neoplasia, and benign

15   prostate lesions including benign prostatic hyperplasia. In addition, the system according to the invention, can treat apparently healthy tissue in order to prevent the occurrence or re-occurrence of cancerous or benign conditions.

In the preferred embodiment, an E-field feedback probe **175** can be inserted to an appropriate depth in the tissue of prostate **220** that is to be treated. Insertion of E-field

20   feedback probe **175** may be achieved under the guidance of an ultrasound transducer. Means for setting the initial energy phase delivered to each applicator **110,111** includes E-field feedback signals **450** from the E-field probe **175** and computer **250** with an appropriate algorithm in order to focus the energy radiation at the inserted E-field probe **175**. Preferably, the E-field probe **175** is used with an adaptive phased array fast-acceleration gradient search

algorithm, as disclosed in U.S. Pat. No. 5,810,888 to Fenn, to target the energy radiation at

the tumor site **190**.

In addition, the system according to the invention includes means for setting the initial

energy or microwave power delivered to each energy applicator, and means for monitoring

5   the temperatures of walls of the urethra and rectum adjacent the prostate that is to be treated

to ensure that those walls are not overheated. The means for monitoring urethral and rectal

walls may include temperature feedback sensors **410** that are inserted non-invasively against

the urethral and rectal walls (**215, 216**) in order to monitor the temperatures of the urethral

and rectum walls adjacent the prostate tissue. Temperature feedback sensors **410** send

10   temperature feedback signals **400** to computer **250** where signals **400** are used to adjust the

relative microwave power level that is to be delivered to applicators **110, 111** to heat the

tumor or tissue at focus **190**.

Preferably, the design of the transurethral and transrectal energy applicators, which

preferably are microwave applicators, is according to U.S. Pat. No. 5,007,437 to Sterzer. The

15   transrectal applicator, in particular, may use a reflector or a phased array to direct microwave

energy preferentially towards the prostate. The applicators can be noninvasive applicators

such as waveguide, monopole, or dipole antennas, or interstitial applicators such as monopole

or dipole antennas. In a preferred embodiment, the applicators can be driven coherently as a

phased array. In addition, multiple applicators surrounding the prostate that can be driven

20   non-coherently in a multiple frequency array can be used to selectively heat the prostate

tissue.

Preferably, the body or prostate **220** is compressed between two compression balloons

112, 113, which surround transurethral and transrectal applicators **110, 111**, respectively.

Compression balloons **112, 113** can be inflated with distilled or deionized water. In the

alternative, the compression balloons 112, 113 can be inflated pneumatically or by other

known means to inflate balloons. Compression balloons 112, 113 are made from a material

such as latex that is transparent to microwaves. In addition to immobilizing the prostate

tissue and fixing the positions of the applicators, prostate compression has a number of

5   potential advantages for hyperthermia treatments. Utilization of prostate compression results

in less penetration depth required to achieve deep microwave heating and reduces blood flow,

which also improves the ability to heat tissue.

Injection of a local anesthetic drug such as lidocaine with ephinephrine, or anti-

angiogenesis drug into the prostate tissue can be used to reduce blood flow as well. In a

10   preferred method according to the invention, both the prostate compression technique and

drug therapy for reducing blood flow in the prostate gland are used to allow rapid heating of

the microscopic, malignant and benign cancer cells. This preferred method can be

administered as a preventative means for cancer and BPH when PSA levels are less than 4,

and for BPH when the AUA Symptom Index scores less than 13.

15   Compressing the prostate from the inside and outside of the prostate moves the

surface of the prostate gland farther from the microwave applicator radiators, which helps to

reduce superficial hot spots. In a preferred embodiment, the applicator would have a fluid

filled cavity that would improve coupling of the microwave energy from the applicator to

tissue to be treated. Cooling of the fluid, such as distilled or deionized water, within the

20   transurethral and transrectal applicators or applicator balloons during hyperthermia treatments

helps avoid the potential for developing hot spots in the urethra 205 and rectum 210 thereby

protecting the urethral and rectal walls from overheating.

Prior to the adaptive phased array hyperthermia treatment, the prostate is compressed

between compression balloons 112, 113 and a single invasive E-field feedback probe 175 is

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inserted within the central tissue site (focus 190) in the prostate, parallel to the polarization of

the microwave applicators 110, 111. The microwave applicators 110, 111 are either

monopole or dipole antenna radiators of straight or helical shape. E-field probe 175 is used to

monitor the focal E-field amplitude as the phase shifters are adjusted for maximum feedback

5   signal using an adaptive phased array gradient search algorithm. Noninvasive temperature

sensors 410 monitor the urethral and rectal wall temperatures at positions 184, 185,

respectively, and these signals are individually transmitted to the computer as temperature

feedback signals 400.

The tips of temperature sensors 410 can be attached to the outside of the transurethral

10   and transrectal compression balloons 112, 113 as long as the tips are thermally insulated. The

thermal isolation can be achieved by mounting a thin pad (not shown) between the

temperature probe and the outside surface of the balloon, from the effects of the cooling fluid

contained with the compression balloons. The dual-applicator adaptive phased array of the

invention together with the E-field feedback probe allows the phase shifters to be adjusted so

15   that a concentrated E-field can be generated permitting focused heating in tissue at the

appropriate depth.

Preferably, temperature sensors 410 are non-invasively inserted through the openings

of the urethra 205 and rectum 210 so that the sensors 410 are in pressure contact with the

respective, urethral and rectal wall. Thus, as shown in Figure 1, two temperature feedback

20   probe sensors 410 are located in the urethra 205 and rectum 210, respectively and produce

temperature feedback signals 400. Two microwave water-cooled catheters 300, 301 with

microwave applicators 110, 111, respectively, are positioned in the urethra 205 and rectum

210. Transurethral catheter 300 contains a Foley balloon 118 that is air inflated in the bladder

202 to fix the microwave applicator **110** in the correct position with respect to the target area of the prostate.

For coherent treatments, an oscillator **105** is divided at node **107** and feeds phase shifters **120**. Oscillator **105** in a preferred method is a microwave energy source at

5   approximately 915 MHz. The phase control signal **125** controls the phase of the microwave signal over the range of 0 to 360 electrical degrees. The microwave signal from each phase shifter **120** feeds into microwave power amplifiers **130**. The resultant microwave signal is controlled by a computer-generated control signal **135**, which sets the initial microwave power level delivered to each microwave applicator. Microwave signals **150** in the form of

10   coherent 915 MHz microwave power is delivered by the microwave power amplifier **130** to the two applicators **110, 111** while phase shifters **120** in each channel are adjusted to maximize and focus the microwave energy at the E-field probe sensor **175** so that microwave power is maximized at the focus position **190**. The treatment then begins.

In another embodiment, the means for monitoring temperature of the prostate is a

15   temperature probe that is inserted at an appropriate depth in the prostate tissue. In this case, after the means for setting the initial relative energy phase delivered to each applicator is focussed at the E-field probe **175**, the E-field probe can be removed and the temperature probe **176** can be inserted in its place temperature at an appropriate depth in the prostate tissue.

20   In yet another embodiment envisioned by the invention, a second temperature monitoring means, in addition to the non-invasive temperature sensors in pressure contact with the walls of the urethra and the rectum, is provided. The second temperature monitoring means is the invasive temperature probe **176** that is inserted in the prostate tissue in the same spot from which the E-field probe **175** removed.

The system and method according to the invention enable all of the treated prostate carcinomas, pre-cancerous cells, and benign lesions to be destroyed when the desired total microwave energy dose has been delivered to the microwave applicators while avoiding damage to the normal tissue of the prostate.

5   For non-coherent treatments, as shown in Figure 2, separate oscillators 105, which preferably operate at 915 MHz, feed the two microwave power amplifiers 130 that are computer controlled and deliver microwave power to the two applicators 110, 111.

During the hyperthermia treatment, the microwave signals 150 and power level delivered to each of the applicators is measured as a power feedback signal 500, which is sent

10   to a microprocessor or computer 250 such as a PC. The power control signal of the power amplifiers 130 is adjusted either manually or automatically to control the urethra and rectum temperatures, as well as, the equivalent thermal dose delivered to the prostate tissue. The sensors 410 measure the urethral and rectal wall temperatures and the power control signal 135 is adjusted based on the sensed temperature to avoid high temperatures that could cause

15   burns or blisters. The amount of compression realized by compression balloons 112, 113 is adjusted as necessary during treatment to provide patient comfort. Each time the prostate compression is adjusted, for coherent treatments, the phase shifters 120 are readjusted/refocused so that the E-field probe 175 receives maximum power.

According to the system according to the invention, means for monitoring the

20   microwave energy delivered to the microwave applicators 110,111 monitor the delivered energy/power during treatment and when the desired total microwave energy has been delivered by the microwave applicators 110,111 to the prostate, means for terminating the treatment turn off the energy radiation to the applicators. That is, the system and method according to the invention automatically turns off the energy that is being delivered to the

prostate, thereby completing the hyperthermia treatment when a desired total microwave

energy dose has been delivered to the prostate 220. In a preferred embodiment, the total

microwave energy dose produces a total equivalent thermal dose in prostate tumors, which is

approximately between 60 minutes and 400 minutes relative to 43 degrees Celsius. The total

5   microwave energy, since the start of the treatment, delivered to the microwave applicators is

computed within computer 250 and can be displayed on the computer monitor 260 during the

treatment.

As an alternate embodiment, means are provided for monitoring the microwave power

level delivered to the E-field probe 175 to determine when the treatment should be

10   terminated. According to this embodiment, the total microwave energy calculated from the

E-field feedback signal 450 received by the E-field probe 175 is used to control the length of

the treatment. This E-field feedback signal 450 can be useful for both coherent and non-

coherent treatments. In order to determine the effectiveness of the treatment, the prostate

tissue is imaged with one of x-ray and magnetic resonance imaging before and after the

15   microwave total energy dose is administered, as well as pathological results from needle

biopsy of the prostate tissues.

For coherent treatments, the single invasive E-field probe 175 can be replaced with

two noninvasive E-field sensors at fixed positions 186, 187 within the urethra and rectum,

respectively. The E-field sensors are inserted in the natural openings of the urethra 205, and

20   rectum 210 and fixed in a position that is suitable to heat the tumor or healthy tissue. E-field

sensors can be attached to the urethral and rectal walls at positions 186, 187, but they do not

have to be in contact with the urethral and rectal walls. Ultrasound, x-rays or other known E-

field monitoring device can verify the suitable E-field sensor positions. The total power

measured by the two noninvasive E-field sensors is minimized (as in U.S. Pat. No. 5,810,888)

by adjusting the microwave phase shifters **120**, to create a focused E-field in the central

portion of the prostate, or the area of the prostate to be treated.

With this embodiment, there is no risk of infection due to an inserted probe, no risk of

scarring of the skin by a procedure which requires nicking the skin and inserting a probe, and

5   no risk of spreading cancer cells as an inserted E-field probe is not used. The E-field sensors

merely are fixed within the urethra and rectum and thus, do not pass through a tumor bed

thereby reducing the possibility of inadvertently seeding viable cancer cells during a surgical

procedure, thus reducing local recurrences of the cancer in surrounding tissues. Likewise,

since both the temperature and E-field sensors can be placed in the urethra **205** and rectum

10   **210** according to this method, the instant invention would work well when there is no defined

single area in the prostate such as in the treatment of microscopic prostate disease.

Preferably, each channel (on either side of node **107**) of the phased array contains an

electronically-variable microwave power amplifier **130** (0 to 100 W), an

electronically-variable phase shifter **120** (0 to 360 degrees), and water-cooled microwave

15   applicators **110, 111**.

While the preferred embodiment discloses microwave energy at approximately 915

MHz, the frequency of the microwave energy may be between 100 MHz and 10 GHz. The

frequency of the microwave energy could be selected from the range of 902 MHz and 928

MHz. In fact, lower frequencies of energy may be used to ablate or prevent cancerous tissue.

20   In a preferred embodiment, the initial microwave power delivered to each applicator

is between 0 and 70 Watts, preferably between 20 and 60 Watts. Over the entire treatment of

the tissue, the microwave power delivered to each applicator may be adjusted over the range

of 0-150 Watts to deliver the desired microwave energy dose and to avoid overheating the

urethra and rectum. In addition, the relative microwave power delivered to the two

microwave applicators is adjusted between -180 degrees and 180 degrees before and during

the treatment to create a focussed field in the prostate tissue. Typically, more microwave

power is required for non-coherent applicator treatments than for coherent applicator

treatments.

5   In a preferred embodiment, a 0.9-mm outside-diameter (OD) invasive E-field coaxial

monopole probe (semi-rigid RG-034), with the center conductor extended 1 cm, can be used

as E-field probe **175** to measure the amplitude of the electric field directed to the tissue and to

provide the feedback signal **450** used to determine the necessary relative phase for the

electronic phase shifters prior to treatment. Coaxially-fed monopole probes of this type have

10   been used to make accurate measurements of linearly polarized electric fields in compressed

breast phantoms (Fenn et al., International Symposium on Electromagnetic Compatibility 17-

19 May 1994 pp. 566-569). This linearly-polarized E-field probe is inserted within a 1.6 mm

OD teflon catheter. Thermocouple probes (Physitemp Instruments, Inc., Type T copper-

constantan, enclosed within a 0.6 mm OD teflon sheath) can be used to measure the local

15   temperature in the tumor during treatment. These temperature probes have a response time of

100 ms with an accuracy of 0.1° C. Fiber-optic temperature probes may also be used.

           The E-field probe **175** is used with the adaptive phased array fast-acceleration

gradient search algorithm, as disclosed in U.S. Pat. No. 5,810,888 to Fenn, to target the

microwave radiation at the tumor site. The temperature sensed by the invasive temperature

20   probe **175** in the tumor could be used as a real-time feedback signal during the treatment.

This feedback signal **450** could be used to control the microwave output power level of the

variable power amplifiers, which set and maintain the focal temperature at the tumor site in

the range of 43 to 46° C. The power and phase delivered to the two channels of the phased

array are adjusted adaptively using digital-to-analog converters under computer control.

Total Microwave Energy Dose can be used to estimate the required heating time. That is, Applicants realized that a non-invasive equivalent temperature sensing means could replace the invasive temperature probes, and that the Total Microwave Energy Dose reliably could be used to control the duration of treatment. The prostate compression, as mentioned

5   earlier, reduces blood flow, which likely eliminates the effects of blood flow on the required microwave energy for treatment, and may reduce the variation in microwave energy that can be expected in microwave treatments.

Accordingly to a preferred embodiment, the total microwave energy delivered to the waveguide applicators to determine completion of the treatment is between 25 kilo Joules and

10   250 kilo Joules. The total amount of microwave energy dose that would destroy any cancerous or precancerous tissue would be approximately 175 kilo Joules. But, under certain conditions, the required microwave energy dose may be as low as 25 kilo Joules.

As applicants recognized, compression of a body that results in a smaller thickness may require less microwave energy dose (compared to a compression that results in a larger

15   thickness) for effective treatments in preventing or destroying cancerous, pre-cancerous or benign lesions. It is important to select an appropriate initial microwave power level (P_1,P_2) delivered to each applicator as well as the proper microwave phase between the two applicators to focus the energy at the area to be treated.

During hyperthermia treatment, it is necessary to monitor the urethral and rectal wall

20   temperatures so that they do not rise significantly above about 41 degrees Celsius for more than several minutes. The equivalent thermal dose for the urethral and rectal wall sensors can be calculated (Sapareto, et al., International Journal of Radiation Oncology Biology Physics, Vol. 10, pp. 787-800, 1984) and can be used as a feedback signal. Typically, it is necessary to avoid delivering more than a few equivalent minutes thermal dose. Avoiding high urethral

and rectal temperatures according to the invention is accomplished by adjusting the

individual powers (P_1, P_2) delivered to the applicators during treatment either by manual or

automatic computer control.

Doppler ultrasound can be used to measure blood flow in tumors and surrounding

5   prostate tissue, before and during treatment to plan and adjust the microwave energy dose.

For example, less energy dose is required when the tumor blood flow rate is reduced which

can occur when the prostate is compressed and/or the tumor is heated to therapeutic

temperatures. Alternatively, the water content and dielectric parameters of prostate tumor

tissue from needle biopsies could be measured and used to determine, prior to the treatment,

10   the required microwave energy dose. For example, higher water content and higher electrical

conductivity in the tumor would reduce the amount of required microwave energy dose. In

addition to the above variables, the size of the tumor impacts the required microwave energy

dose. Larger tumors are more difficult to heat than smaller tumors and require a larger

microwave energy dose. An initial treatment planning session involving a low-dose delivery

15   of microwave energy to assess the heatability of the tumor, followed by a complete treatment

at the full required microwave energy dose may be performed.

Simplified Microwave Radiation Theory

Microwave energy from hyperthermia applicators, in the near field of a body, radiates

as a spherical wave with the electric-field amplitude varying, in part, as the inverse of the

20   radial distance r from the applicator. Additionally, the amplitude decays as an exponential

function of the product of the attenuation constant α of the body tissue and the distance d

traversed (or depth) within the body as indicated in Figure 1. The electric-field phase varies

linearly with distance according to the product of the phase propagation constant β and

distance d. For simplicity, dual-opposing applicators are analyzed here under the assumption

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that the applicator radiation is approximated by a plane wave. Mathematically, the

plane-wave electric field versus depth in tissue is given by $E(d)=E_o \exp(-\alpha d) \exp(-i\beta d)$, where

E_o is the surface electric field (in general represented by an amplitude and phase angle), and i

is the imaginary number (Field and Hand, An Introduction to the Practical Aspects of Clinical

5   Hyperthermia , Taylor & Francis, New York p. 263, 1990).

Plane-wave electromagnetic energy, at the microwave frequency of 915 MHz,

attenuates at a rate of about 3 dB per cm in high-water content tissue, such as prostate tissue.

Thus, a single radiating applicator has a significant fraction of its microwave energy absorbed

by intervening superficial body tissue compared to the energy that irradiates deep tissue,

10   likely creating a hot spot in superficial tissue. Since surface cooling with either air or water

protects tissue only to a maximum depth of about 0.25 to 0.5 cm, in order to avoid hot spots,

it is necessary to introduce a second phase-coherent applicator, having the same microwave

radiation amplitude as the first applicator. The second phase-coherent applicator can

theoretically increase the power (and hence the energy) delivered to deep tissue by a factor of

15   four compared to a single applicator (Field and Hand, p. 290, 1990).

The phase characteristics of the electromagnetic radiation from two or more

applicators (known as a phased array) can have a pronounced affect on the distribution of

power delivered to different tissues. The relative specific absorption rate (SAR) in

homogeneous tissue is approximated by the square of the electric-field amplitude $|E|^2$. The

20   SAR is proportional to the rise in temperature over a given time interval. A simplified case,

homogeneous prostate tissue, in which the microwave radiation is focused at a central tissue

site, is described in detail below. As described in an article by Fenn et al., International

Symposium on Electromagnetic Compatibility, Sendai, Japan, Vol. 10, No. 2, May 17-19,

1994, pp. 566-569, the effects of multiple microwave signal reflections within the phantom can be ignored.

The wavelength in homogeneous normal prostate tissue (with approximate dielectric constant 50 and electrical conductivity 1.3 S/m) is approximately 4.5 cm at 915 MHz, and the

5   microwave loss is 3 dB/cm. The attenuation constant α is 0.34 radians/cm and the propagation constant β is 1.4 radians/cm (or 80 degrees/cm). (For a compressed prostate thickness of 2.25 cm, the electric field of a single applicator radiating on the left side is E_o at the surface of the prostate, $-i0.7E_o$ (where i represents a 90-degree phase shift) at the central position (1.125 cm deep), and $-0.5E_o$ at the right surface. Combining two phase coherent

10   applicators yields an electric-field value of $0.5E_o$ on both surfaces and $-i1.4E_o$ at the central position (1.125 cm depth). Thus, for the compressed prostate, by squaring the above coherent E-fields to compute SAR, there is a significantly lower SAR at the surface, by about a factor of 2.0 compared to the central SAR. The 180-degree phase shift experienced by the microwave field transmitted through 2.25 cm of prostate tissue, partly cancels or nulls the

15   field entering the tissue with 0-degree phase shift. Due to destructive interference of the microwaves away from the central focus lower temperatures in the superficial prostate tissues would be expected. Measurement and enforcement of lower SAR on the opposing surfaces effectively focuses the microwave energy deep in the prostate. In cases where it is desirable to radiate the superficial or peripheral zone prostate tissues more strongly, the compression

20   thickness can be larger than 2.25 cm so that the propagating wave phase delay is longer and the two waves do not cancel at the surface, or only one of the transurethral or transrectal applicators (especially the transrectal applicator) can be used to heat the prostate.

Repeating the above calculation, but now for non-coherent applicators, for a compressed prostate thickness of 2.25 cm, the electric field of a single applicator radiating on

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the left side is E_o at the surface of the prostate, $-i0.7E_o$ (where i represents a 90-degree phase

shift) at the central position (1.125 cm deep), and $-0.5E_o$ at the right surface. Combining two

applicators non-coherently, by squaring the individual E-fields and adding them, yields a

SAR value of $1.5E_o{}^2$ on both surfaces and $0.98\,E_o{}^2$ at the central position (1.125 cm depth).

5   Thus, for the compressed prostate, by squaring the above non-coherent E-fields to compute

SAR, there is a significantly higher SAR at the surface, by about a factor of 1.5 compared to

the central SAR. For this reason, it is more difficult to heat deep prostate tissue with the non-

coherent array compared to the coherent array. However, as mentioned earlier, for prostate

cancer treatment some of the prostate cancer cells can be located close to the rectum and non-

10   coherent treatment may provide adequate heating.

The adaptive phased array system according to the invention uses two microwave

channels, fed by a common oscillator 105, containing two electronically adjustable phase

shifters 120 to focus the microwave energy at an E-field feedback probe 175. This inventive

adaptive phased array system has significant advantage over a non-adaptive phased array. A

15   non-adaptive phased array with two channels could, in theory, produce a null, a maximum, or

an intermediate value of E-field depending on whether the two waves are 180 degrees out-of-

phase, completely in-phase, or partly out-of-phase, respectively. That is, the microwave

phase delivered to the microwave applicators, according to the invention, can be adjusted

between -180 degrees and 180 degrees before and during the treatment to create a focused

20   field in the prostate tissue.

The adaptive phased array according to the invention automatically focuses the E-field

in the presence of all scattering structures in the tissue. Thus, the adaptive phased array

according to the invention should provide more reliable deep focused heating compared to

manually adjusted or pre-treatment planning controlled phased arrays as described in U.S.

Patent No. 4,589,423 to Turner. Furthermore, the adaptive phased array system according to

the invention does not use an invasive temperature probe, which could scatter or alter the E-

field at the tumor site.

<u>Calculation of Microwave Energy</u>

5   Electrical energy consumption is commonly expressed in units of kilowatt hours.

Mathematically, the expression for the microwave energy W delivered by an applicator is

given by (Vitrogan, Elements of Electric and Magnetic Circuits, Rinehart Press, San

Francisco, pp. 31-34, 1971):

$$W = \Delta t \Sigma P_i. \quad (1)$$

10   In the above equation, Δt represents the constant intervals (in seconds) in which microwave

power is measured and the summation Σ is over the complete treatment interval with the

power (in Watts) in the ith interval denoted by P_i

The microwave energy W has units of watt-seconds, which is also designated as

Joules. For example, in three consecutive 60-second intervals if the microwave power is 30

15   watts, 50 watts, 60 watts, respectively, the total microwave energy delivered in 180 seconds is

calculated as $W = 60 (30 + 50 + 60) = 8,400$ watt-seconds $= 8,400$ Joules $= 8.4$ kJ.

To understand better the focused energy per unit time W' (where ' denotes prime)

deposited at a central position in homogeneous prostate tissue of varying thickness (denoted

by D) by dual-opposing applicators, consider the following calculation for coherent

20   treatments. Let P_1 and P_2 be the power delivered to the two applicators, respectively. The

electric field radiated by each applicator is proportional to the square root of the power

delivered to the applicator. Assuming symmetry, the radiated fields are in-phase at the

central focused position from the two applicators. Assuming equal power from each

applicator, that is, $P_1 = P_2 = P$, and plane wave illumination, then the focused energy per unit

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time at the central depth is expressed as

$$W'(D) = |E|^2 = 4P \exp(-\alpha D) . \qquad (2)$$

Calculation of Equivalent Thermal Dose

The cumulative or total equivalent thermal dose relative to 43 degrees Celsius is

calculated as a summation (Sapareto, et al., International Journal of Radiation Oncology

Biology Physics, Vol. 10, pp. 787-800, 1984):

$$t_{43°C} \text{ equivalent minutes } = \Delta t \Sigma R^{(43-T)}, \qquad (3)$$

where Σ is the summation over a series of temperature measurements during the treatment, T

is the series of temperature measurements (T_1, T_2, T_3, ...), Δt is the constant interval of time

(units of seconds and converted to minutes) between measurements, R is equal to 0.5 if

$T>43°$ C and R is equal to 0.25 if $T<43°$ C. The equivalent thermal dose calculation is useful

for assessing any possible heat damage to the prostate tissues, urethra and rectum.

Equivalents

While this invention has been particularly shown and described with reference to

preferred embodiments thereof, it will be understood by those skilled in the art that various

changes in form and details may be made therein without departing from the spirit and scope

of the invention as defined by the appended claims. For instance, although the hyperthermia

system described herein is with respect to the treatment of prostate carcinomas and benign

prostate lesions, the invention is applicable to the treatment of other types of cancers such as

breast, liver, lung, and ovarian. It is also understood that larger or smaller numbers of array

antenna applicators, or single antenna applicators such as transurethral or transrectal, may be

used with similar results. Some of the methods and techniques described herein are also

applicable to ultrasound hyperthermia system particularly the use of energy dose for feedback

control. The system according to the invention can be used to enhance radiation therapy or

for targeted drug delivery and/or targeted gene delivery using thermosensitive liposomes or

for targeted gene therapy. The invention is also applicable to non-medical hyperthermia

systems, such as those used for industrial heating.

We claim:

1. A system for treating of one of cancerous, pre-cancerous, pre-benign and benign conditions of a prostate by irradiation of the prostate with concentrated energy, the

5 system comprising:

a) means for monitoring temperatures of walls of the urethra and rectum adjacent the prostate;

b) at least one energy applicator oriented for irradiating the prostate with energy;

c) means for setting the initial energy power delivered to said at least one energy

10 applicator;

d) means for adjusting the relative energy power delivered to said at least one applicator during treatment based on the monitored urethral and rectal wall temperatures;

e) means for monitoring the energy delivered to said at least one energy applicator; and

15 f) means for automatically terminating the treatment when a desired total energy dose has been delivered by said at least one microwave applicator to the prostate.

2. The system according to claim 1, wherein the concentrated energy is microwave energy and further comprising:

20 an E-field probe for insertion to an appropriate depth in tissue of the prostate; and

means for setting the initial relative microwave phase delivered to each applicator to focus the microwave energy at the E-field probe positioned in the prostate tissue.

3. The system according to claim 2, wherein the E-field probe is inserted into the

25 prostate tissue under ultrasound guidance to the central depth of the prostate tissue or in a prostate lesion.

4. The system according to claim 1, wherein the means for monitoring the urethral and rectal wall temperatures include temperature probes in pressure contact with the

30 walls of the urethra and rectum.

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5.   The system according to claim 1, wherein said at least one energy applicator is oriented in at least one of the urethra and rectum and further comprising means for compressing the prostate and for fixing positions of said at least one energy applicator.

5   6.   The system according to claim 5, wherein the means for compressing the prostate and for fixing positions of the applicators includes a balloon that is inflated with one of distilled and deionized water, said balloon being inserted in at least one of the urethra and rectum.

10   7.   The system according to claim 1, wherein the concentrated energy is one of microwave, ultrasound, radiofrequency, and laser energy and wherein one or more coherent or non-coherent microwave applicators surround the prostate to selectively irradiate the prostate tissue with microwave energy to treat one of cancerous, pre-cancerous, benign and pre-benign conditions of the prostate.

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8.   The system according to claim 1, wherein the concentrated energy is one of microwave, ultrasound, radiofrequency, and laser energy and wherein said at least one energy applicator is inserted interstitially within the prostate to selectively irradiate the prostate tissue with concentrated energy to treat cancerous, pre-cancerous, and benign conditions of

20   the prostate.

9.   The system according to claim 1, wherein the cancerous conditions of the prostate include one of adenocarcinoma, carcinosarcoma, rhabdomyosarcoma, chondrosarcoma, and osteosarcoma, and pre-cancerous conditions include one of prostatic

25   intraepithelial neoplasia, and benign prostate lesions including benign prostatic hyperplasia.

10.   The system according to claim 1, wherein the concentrated energy is microwave energy and said at least one energy applicator is oriented in at least one of the urethra and rectum, and further comprising means for cooling the microwave applicators in

30   the urethra and rectum with water; and means for adjusting the water cooling temperature for

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the transurethral and transrectal applicators to protect the urethra and rectum from overheating.

11.   The system according to claim 1, wherein the concentrated energy is microwave energy and further comprising a fluid-filled catheter wherein said at least one microwave applicator is disposed in the fluid-filled catheter and the fluid-filled catheter couples microwave energy from said at least one applicator to the tissue to be treated.

12.   The system according to claim 1, wherein the concentrated energy is microwave energy and the frequency of the microwave energy is between 100 MHz and 10 GHz.

13.   The system according to claim 1, wherein the concentrated energy is microwave energy said at least one microwave applicator is two microwave applicators oriented in the urethra and rectum, respectively; and further comprising means for adjusting the relative microwave phase delivered to the two microwave applicators, the relative microwave phase being adjusted between −180 degrees and 180 degrees before and during the treatment to create a focused field in the prostate tissue.

14.   The system according to claim 1, wherein the concentrated energy is microwave energy and the initial microwave power delivered to said at least one applicator is between 0 Watts and 70 Watts.

15.   The system according to claim 1, wherein the concentrated energy is microwave energy and the means for adjusting the microwave power delivered to said at least one applicator adjusts the microwave power over the range of 0 to 150 Watts during the treatment to deliver the desired microwave energy dose and to avoid overheating the healthy tissue and walls surrounding the area to be treated.

16.   The system according to claim 1, wherein the concentrated energy is microwave energy and further comprising means for determining the total microwave energy delivered to said at least one microwave applicator and means for displaying the total microwave energy in real time during the treatment.

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17.   The system according to claim 1, wherein the concentrated energy is microwave energy and the total microwave energy delivered to said at least one applicator for the complete treatment is between 25 kilo Joules and 250 kilo Joules.

10   18.   The system according to claim 2, wherein the means for monitoring temperatures of the urethral and rectal walls is a temperature probe that is inserted at an appropriate depth in the prostate tissue, said temperature probe being inserted in the prostate at the same place the E-field probe was inserted.

15   19.   The system according to claim 1, wherein the concentrated energy is microwave energy and the total microwave energy dose produces a total equivalent thermal dose in prostate tumors which is approximately between 60 minutes and 400 minutes relative to 43 degrees Celsius.

20   20.   The system according to claim 2, further comprising means for monitoring the microwave power level delivered to the E-field probe, wherein the total microwave energy received by the E-field probe is used as feedback to determine the length of treatment.

21.   The system of claim 1, wherein all of the treated prostate carcinomas, pre-
25   cancerous cells, and benign lesions are destroyed when the desired total energy dose has been delivered to said at least one microwave applicator while damage to the normal tissue of the prostate is avoided.

22.   The system of claim 4, further comprising second means for monitoring the urethral and rectal wall temperatures, said second temperature monitoring means being an inserted temperature probe.

5   23.   The system of claim 1, further comprising two non-invasive E-field sensors positioned on urethral and rectal wall surfaces adjacent the prostate; and means for setting and adjusting the initial relative energy phase delivered to said at least one applicator to minimize the energy at the E-field sensors positioned on urethal and rectal wall surfaces adjacent the prostate to focus the energy at the prostate tissue to be treated.

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24.   A method for preventing the occurrence or recurrence of cancerous or benign conditions in a prostate by one of selective heating of or irradiating tissue of the prostate with concentrated energy, the method comprising the steps of:

a)   Monitoring temperatures of walls of the urethra and rectum adjacent the

15   prostate;

b)   Orienting at least one energy applicator for irradiating the prostate with energy;

c)   Adjusting the relative power to be delivered to said at least one applicator during treatment based on the monitored wall temperatures;

20   d)   Monitoring the energy delivered to said at least one energy applicator; and

e)   Automatically completing the treatment when a desired total energy dose has been delivered by the energy applicators to the treated tissue.

25.   A method according to claim 24, wherein the concentrated energy is one of

25   microwave, ultrasound, radiofrequency, and laser energy and wherein the method is used when a prostate specific antigen level is less than 4.0 ng/ml in order to prevent the prostate specific antigen level from rising above 4.0 ng/ml.

26.   A method according to claim 24, wherein benign prostatic hyperplasia is

30   treated with one of concentrated or focused microwave, ultrasound, radiofrequency, and laser energy and wherein a patient is treated when the AUA symptom index is less than 13.

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27.   The method according to claim 24, wherein, for treating prostate cancer, the concentrated energy is focused microwave energy and when a patient's prostate specific antigen level is greater than 4.0 ng/ml, the patient is treated to reduce the prostate specific antigen level to below 4.0 ng/ml.

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28.   The method according to claim 24, wherein, for treating benign prostatic hyperplasia, the focussed energy is microwave energy and when a patient's AUA symptom index is greater than 13, the patient is treated to reduce the AUA symptom index to below 7.

10   29.   The method according to claim 24, wherein said at least one energy applicator is disposed in at least one of the urethra and rectum.

30.   The method according to Claim 24, further comprising the steps of:
f)   Inserting an E-field probe to an appropriate depth in tissue of the prostate; and
15   g)   Delivering energy/power with a relative energy phase to said at least one energy applicator to focus the energy at the E-field probe.

31.   The method according to Claim 24, further comprising the steps of:
f)   Positioning two noninvasive E-field sensors on the urethral and rectal walls; and
20   g)   Adjusting the microwave phase delivered to each microwave applicator to minimize the total power received by the E-field urethra and rectal sensors thereby creating a focused field in the prostate.

32.   The method according to claim 24, wherein the step of monitoring
25   temperatures further includes monitoring the temperature at an appropriate depth internally within the prostate tissue, said temperature monitoring step being achieved by means of noninvasive thermometry techniques including one of infrared, laser, ultrasound, electrical impedance tomography, magnetic resonance imaging, and microwave radiometry; and wherein the step of adjusting the relative energy power to be delivered to the prostate is based
30   on the monitored internal temperature, the monitored urethral and rectal wall temperatures,

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and the monitored energy dose.

33.   The method according to claim 24, wherein two or more microwave applicators surrounding the prostate from outside the skin surface of a patient's body, in a

5   ring, to selectively irradiate the prostate tissue with focused energy to treat one of cancerous, pre-cancerous, benign and pre-benign conditions of the prostate.

34.   The method of claim 24, wherein focused microwave radiation is used to enhance one of radiation therapy, targeted drug delivery and targeted gene therapy with or

10   without thermosensitive liposomes for treatment of prostate tumors and other prostate lesions.

35.   A method for treating one of cancerous, pre-cancerous, benign and pre-benign conditions of the prostate by selective irradiation of the prostate tissue with focused

15   microwave energy, the method comprising the steps of:

a)   Inserting an E-field probe to an appropriate depth in the prostate tissue;

b)   Monitoring temperatures of walls of the urethra and rectum adjacent the prostate;

c)   Orienting two microwave applicators in the urethra and rectum for irradiating

20   the prostate with microwave energy;

d)   Delivering microwave energy/power with a relative microwave phase to each applicator to focus the microwave energy at the E-field probe positioned in the prostate tissue;

e)   Adjusting the relative microwave power to be delivered to each applicator

25   during treatment based on the monitored urethral and rectal wall temperatures;

f)   Determining boundary points about the E-field probe to obtain a geometric shape for irradiating the prostate; and

g)   Adjusting the relative phase of the microwave energy applied to each applicator so that the applied focused microwave energy scans the determined geometric

30   shape thereby irradiating a larger area of the prostate.

36.   A method for treating one of cancerous, pre-cancerous, benign and pre-benign conditions of the prostate by selective irradiation of the prostate tissue with focused microwave energy, the method comprising the steps of:

a)   Inserting an E-field probe to an appropriate depth in the prostate tissue;

5   b)   Setting the initial relative microwave phase delivered to each applicator to focus the microwave energy at the E-field probe positioned in the prostate tissue;

c)   After step b, removing the E-field probe and inserting a temperature probe sensor to monitor temperature at an appropriate depth in the prostate tissue;

d)   Monitoring temperatures of walls of the urethra and rectum;

10   e)   Orienting two microwave applicators in the urethra and rectum for irradiating the prostate with microwave energy;

f)   Setting the initial microwave power delivered to each applicator;

g)   Adjusting the relative microwave power to be delivered to the prostate during treatment based on the monitored urethral and rectal temperatures and the monitored

15   microwave energy dose;

h)   Automatically completing the treatment when one of a desired total microwave energy dose and a desired thermal dose has been delivered by the microwave applicators to the prostate.

20   37. A method for treating tumors and other lesions in a body comprising the steps of:

a) compressing prostate tissue;

b) injecting a drug including a local anesthetic with ephinephrine or an anti-angiogenesis drug in an area where a tumor is located, wherein said compression and drug injection reduce blood flow to allow rapid heating of tumors with one of microwave,

25   ultrasound, radiofrequency, and laser energy; and

c) heating the prostate tissue with one of microwave, ultrasound, radiofrequency, and laser energy.

38.   A method for early treatment of cancerous, pre-cancerous, or benign conditions of a prostate by irradiation of the prostate, comprising the steps of:

a)   Determining one of the prostate specific antigen (PSA) level and the American Urological Association (AUA) Symptom Index of a patient; and

5   b)   Heating the patient's prostate with focused microwave energy when one of the PSA level is less than 4.0 ng/ml and the AUA index is less than 13.

39.   A method for treating benign prostatic hyperplasia by irradiation of the prostate with focussed microwave energy, comprising the steps of:

10   a)   orienting at least one microwave applicator in one of the urethra and rectum of a patient; and

b)   heating tissue of the prostate with said at least one microwave applicator whereby the heat of step b) damages the nerves in the prostate area that cause the symptoms of benign prostatic hyperplasia (BPH) thereby reducing pain associated with BPH and lowering the

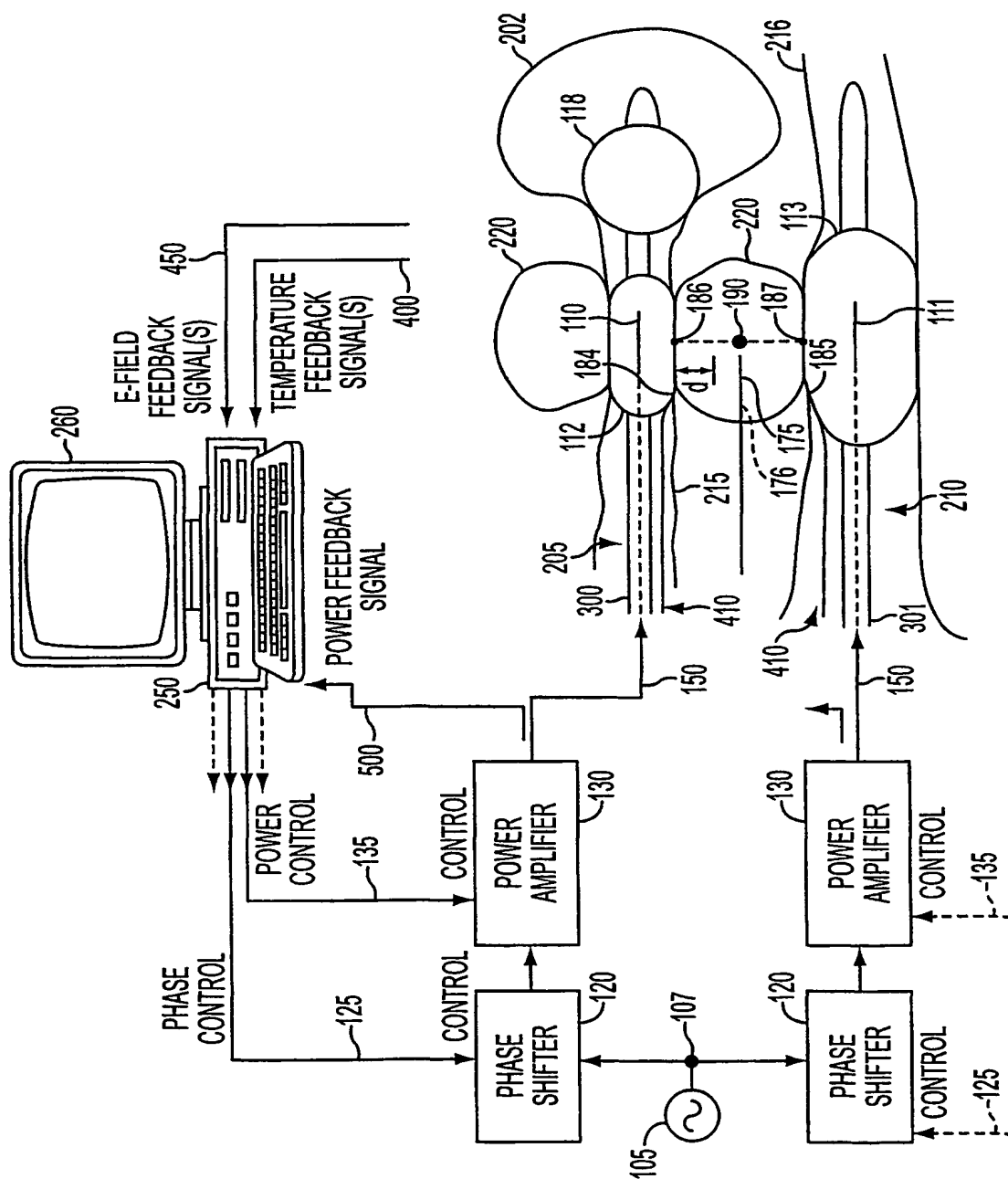15   American Urological Association (AUA) Symptom Index of a patient.

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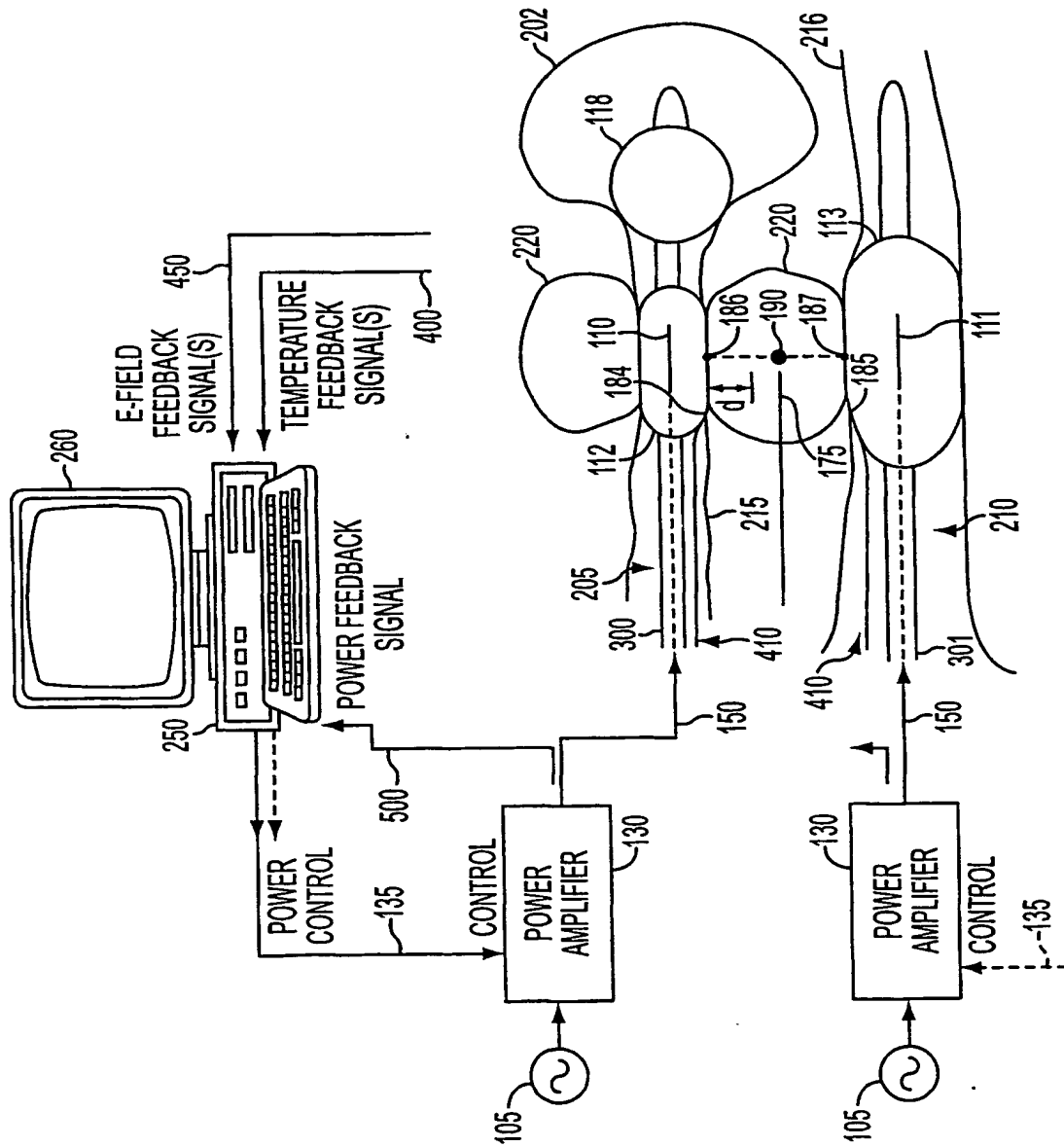

FIG. 1

FIG. 2

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Heating pattern of helical microwave intracavitary oesophageal applicator

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Helical microwave intracavitary oesophageal (HMIO) applicators were designed to operate at frequencies of 433 MHz and 915 MHz. Heating patterns were studied within muscle-equivalent phantom by thermographic camera and fibreoptic thermometers. The results showed that frequency significantly influenced the microwave heating pattern. The 433 MHz applicator had a single power deposition region, the longitudinal specific absorption rate (SAR) distribution appeared to be nearly even, and the maximum SAR value occurred close to the centre of the active length of the applicator. The 915 MHz applicator had two power deposition regions, the peak SAR values occurred at about ¼ and ¾ of the active length respectively. The radial SAR distribution suggested that there is no obvious difference between the 433 MHz and 915 MHz applicators in that the average radial penetration of 50% surface SAR (RP50) was about 0·65 cm. It was also shown that power deposition was axially symmetric for both 433 MHz and 915 MHz HMIO applicators. It is shown that better impedance matching is more important for intracaviary hyperthermia than for external hyperthermia. Choosing HMIO applicators in clinical practice is also discussed.

Key words: 433 MHz and 915 MHz HMIO applicators, thermogram, SAR, heating pattern, intracaviary hyperthermia.

1. Introduction

Hyperthermia is known as an effective adjuvant therapy to treat many kinds of malignant tumours which are refractory by conventional therapies alone (Hahn et al. 1974, Meyer 1984, Overgaard 1985). A variety of microwave intracaviary applicators and application techniques have been described (Sugimachi et al. 1984a, Li et al. 1984, Yamashita et al. 1984, Astrahan et al. 1989a,b). Normally, intracaviary hyperthermia is used in combination with radiotherapy, chemotherapy or surgery. Oesophageal intracaviary hyperthermia has been used clinically for about 10 years (Li et al. 1982, Liu et al. 1983, Sugimachi et al. 1984b). Because of the anatomical site of the oesophagus, it is almost impossible to heat it with external hyperthermia. However, with intracaviary hyperthermia the applicator can touch the lesion directly and almost all of the microwave energy is absorbed by lesions surrounding the applicator, sparing underlying normal tissue and organs from excessive microwave exposure. Certainly, the microwave power needed for intracaviary hyperthermia is much lower than that needed for external hyperthermia.

Helical microwave intracaviary oesophageal (HMIO) applicators were designed to operate at frequencies of 433 MHz and 915 MHz. Heating patterns within static muscle-equivalent phantoms are studied in this paper.

2. Materials and methods

2.1. Microwave power source and applicator

The 50–700 MHz BSD-1000 system (BSD Medical Corp. Salt Lake City, Utah and 915 MHz generator were used as microwave sources.

HMIO applicators were made as follows. Part of the outer conductor from one end of a 125 cm long coaxial cable (RG-223/U 50 Ω) was removed. A 0·07 cm (22-gauge) diameter copper wire was connected to the remaining outer conductor. The copper wire was wound in single and double helical manner on the bare insulator. The antenna was wrapped with three or four layers of Teflon tape; finally, it was put into a plastic tube and sealed at the end with silicon rubber sealant. The active length is from the junction which connected the copper wire and the remaining outer conductor together to the distal end (Figure 1A and B). The optimal operating frequency for each applicator in phantom was determined experimentally by return loss or reflected power measured via a network analyser (Hewlett-Packard Co. Ltd., Santa Rosa, California) or a microwave wattmeter (BIRD Electronic Corporation, Cleveland, Ohio). We adjusted turns, winding position, active length, etc., to obtain the best impedance matching, proper active length (less than 15 cm) and SAR distribution.

2.2. Thermogram and SAR distribution

An HMIO applicator was placed between two 29×26×12 cm muscle-equivalent phantoms as described by Chou et al. (1984). Microwave power (about 100–200 W) was applied for 20 s followed by separation of the phantom and removal of the applicator. Thermograms were taken by a thermographic camera (UTI Company, Sunnyvale, California), which was also used to measure the longitudinal surface temperature distribution of the applicator as well as the radial temperature distribution of the applicator at several longitudinal positions. The thermographic technique was described by Guy (1971) and by Kantor and Ceas (1977).

Radial temperature distribution within the phantom was also measured by Clini-therm thermometer (Clini-therm Corp., Dallas, Texas) with non-perturbing fibreoptic probes (Vaguine et al. 1984). Arrangement was made for eight probes to be 0·5 cm apart along the radial distance starting from the surface of an applicator. Microwave power of 150 W was applied to the applicator for 20 s. Temperatures for each probe were printed every 2 s. Three trials were done for each applicator; the periods between each trial were at least 40 min.

The longitudinal and radial specific absorption rate (SAR) distributions were normalized to the surface maximum SAR value. The SARs were obtained from the rate of temperature increase in a specific volume (Ceas 1982). The average radial penetration of 50% surface SAR (RP50) was calculated from the above results.

3. Results

3.1. Parameters of HMIO applicator

The 433 MHz applicator has an active length of 12·5 cm and an outer diameter of 0·74 cm. Its return loss within muscle-equivalent phantom appeared to be −22 dB with a voltage standing wave rate (VSWR) of 1·17. For the 915 MHz applicator the active length was 14·5 cm, with an outer diameter of 0·84 cm. The return loss for the 915 MHz applicator was −32 dB, with a VSWR of 1·05. The number of windings, spacing between windings, type of winding and pitch angles, etc., are shown in Figure 1B. For both applicators the maximum continuous input power is approximately 100 W.

3.2. Heating pattern

Typical thermograms for 433 MHz and 915 MHz HMIO applicators are shown in Figures 2 and 3, respectively. Their longitudinal relative SAR distributions along the surfaces of applicators are plotted in Figure 5A. The surface maximum SARs were 8·14 W/kg per watt for the 433 MHz applicator and 8·98 W/kg per watt for the 915 MHz
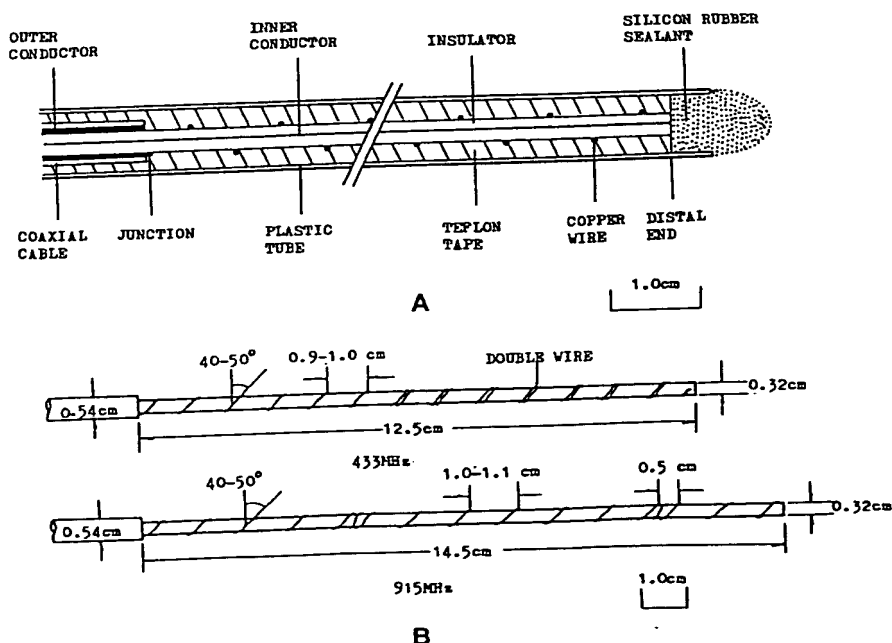
OUTER CONDUCTOR   INNER CONDUCTOR   INSULATOR   SILICON RUBBER SEALANT

COAXIAL CABLE   JUNCTION   PLASTIC TUBE   TEFLON TAPE   COPPER WIRE   DISTAL END

1.0cm

A

40–50°   0.9–1.0 cm   DOUBLE WIRE   0.32cm

0.54cm   12.5cm

433MHz

40–50°   1.0–1.1 cm   0.5 cm   0.32cm

0.54cm   14.5cm

915MHz   1.0cm

B

Figure 1. Cut-out (A) and winding (B) illustration of the HMIO applicators.

Figure 3. Thermograms for 915 MHz HMO applicator. Two power deposition regions are shown. The longitudinal (A) and radial ...
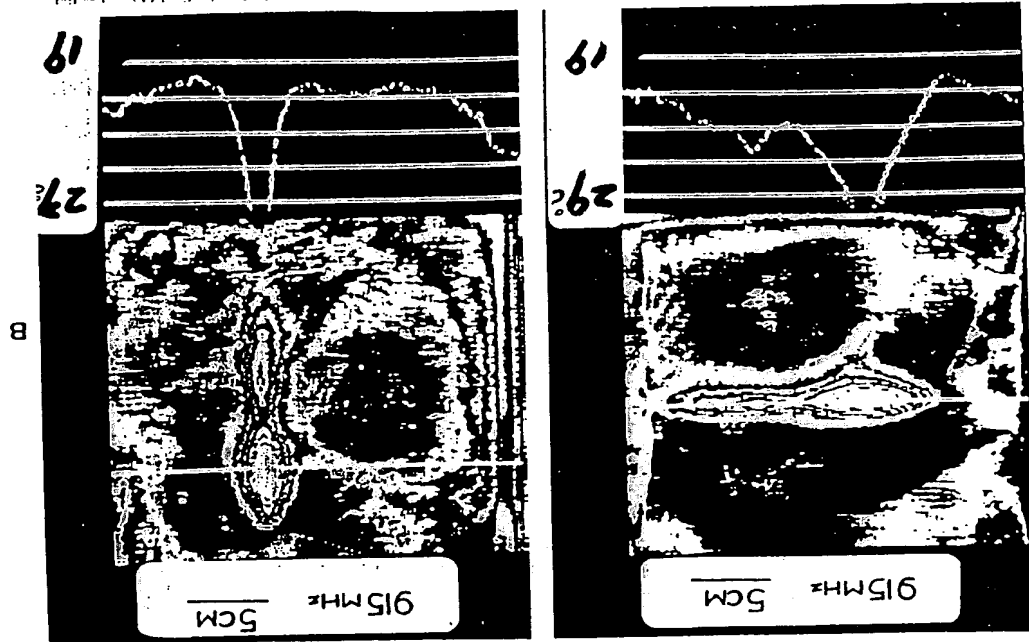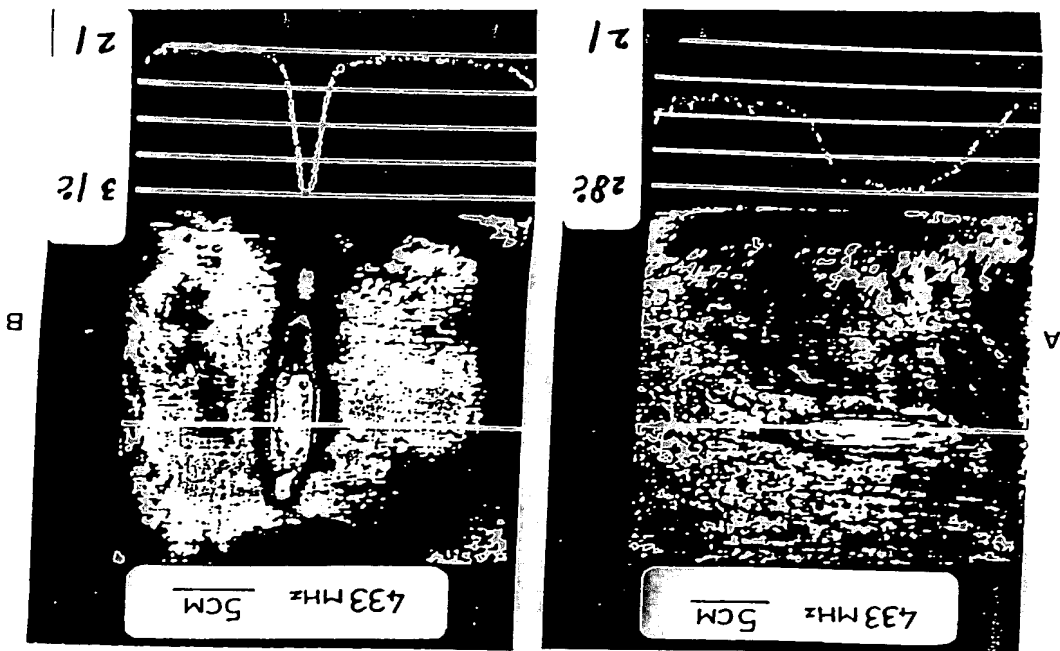

Figure 2. Thermograms for 433 MHz HMO applicator. One power deposition region is shown. The longitudinal (A) and radial (B) temperature distributions are also shown. 97 W (A) and 214 W (B) were applied for 20 s respectively.

applicator. It is evident that the 433 MHz applicator had only one power deposition region, whose longitudinal length was close to the active length of applicator. The peak area appeared to be near the centre of the active length, and its longitudinal relative SAR distribution curve was shown to be nearly even. The heating pattern of the 915 MHz applicator was different from the 433 MHz applicator. It had two power deposition regions, whose combined longitudinal length was also near to the active length of applicator. The two peak areas occurred at about 1/4 and 3/4 of active length respectively.

It was observed that different thermograms (Figure 4A and B) could be obtained by adjusting the winding, active length, etc. In Figure 4A the adjusted 433 MHz applicator has an active length of 13·5 cm, its double wire windings were one turn less than for the 433 MHz applicator in Figure 1B, spacing between windings was about 1·2 cm. Its single power deposition region could be slightly narrowed. In Figure 4B, for the adjusted 915 MHz applicator, only single helical windings were used, spacing between windings was about 1·25 cm, and the number of windings was 11·5. Double power deposition regions still appeared, but with equal peak values. For those adjusted applicators, their longitudinal relative SAR distributions along the surfaces of applicators are plotted in Figure 5B. The surface maximum SARs were 7·56 W/kg per watt for adjusted 915 MHz applicator and 5·66 W/kg per watt for adjusted 433 MHz applicator. Results also showed that for both adjusted 433 MHz and 915 MHz applicators the power deposition regions were axially symmetric.

Figure 6 shows the typical radial relative SAR distribution curves of 433 MHz (Figure 2) and 915 MHz (Figure 3) applicators at several longitudinal positions. For both applicators, relative SAR decays quickly as the radial distance increases, and the rate of decay decreases as the radial distance increases. As for two 433 MHz and three 915 MHz applicators' radial relative SAR distribution curves at several longitudinal positions, the average RP50 values for both of 433 MHz and 915 MHz applicators were close to 0·65 cm.

4. Discussion

The HMIO applicators presented in this paper are simple in structure, easy to assemble, low cost, reliable and flexible. Their power capacity is sufficiently high, and impedance matching excellent, therefore net power is always close to forward power. They are functional intracavitary hyperthermia devices. In China they have been used in the clinic for several years (Hou et al. 1989) combined with a thermocouple thermometer system modified from Chakraborty and Brezovich (1982).

We found that frequency had significant influence on heating pattern, but different windings, pitch angles, turns and active lengths of applicator, etc., could be used to optimize operating frequency, VSWR or heating pattern.

The nature of the heating pattern suggested that HMIO applicators should be chosen according to the type and length of lesion. Usually it is better to place great priority on the 433 MHz applicator, since its longitudinal SAR distribution was shown to be nearly even. For those patients who have longer lesion or two separate lesions, choosing only the 915 MHz applicator or using a 915 MHz and a 433 MHz applicator alternately is probably preferable. Additionally the winding, etc., may need to be adjusted to get more ideal heating patterns in clinical situations.

Since microwave energy is delivered to the lesion through a normal cavity via coaxial cable, good impedance matching is more important than for external hyperthermia. Poor impedance matching might cause the coaxial cable to become hot, and this is undesirable for normal healthy cavity tissues. In our experiments VSWR was always less than 1·5. Impedance matching, however, depends not only on the parameters of the applicator, but also on the characteristics of tissue and the closeness with which the applicator contacts
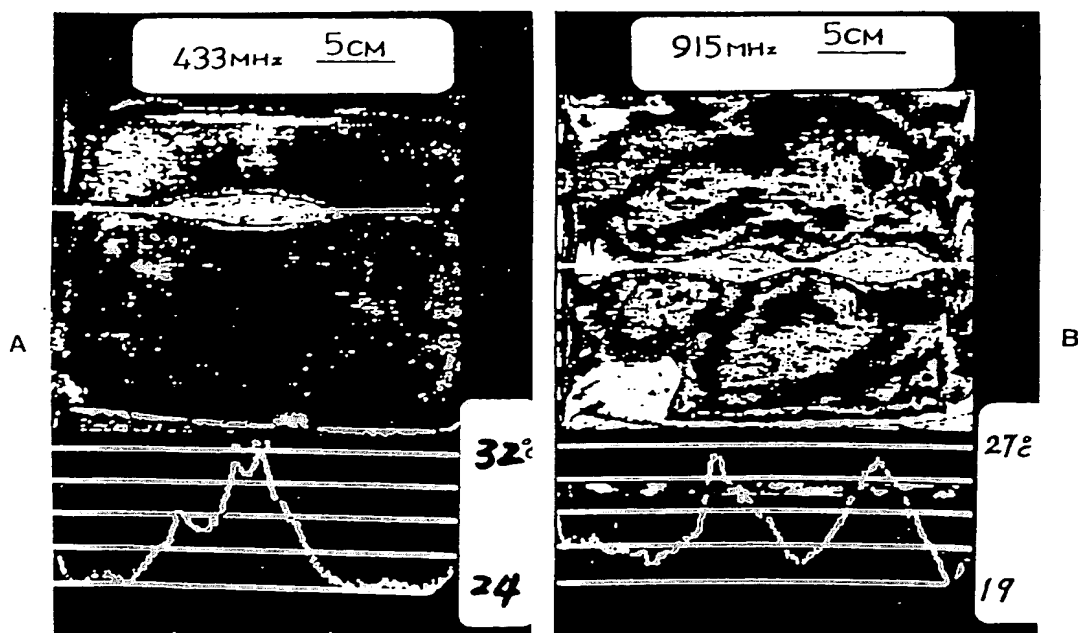
Figure 4. Thermograms for adjusted 433 MHz (A) and 915 MHz (B) HMIO applicators, whose windings etc. were adjusted to be slightly different from Figures 2 and 3 applicators respectively. (A) shows one narrow power deposition region; (B) shows two
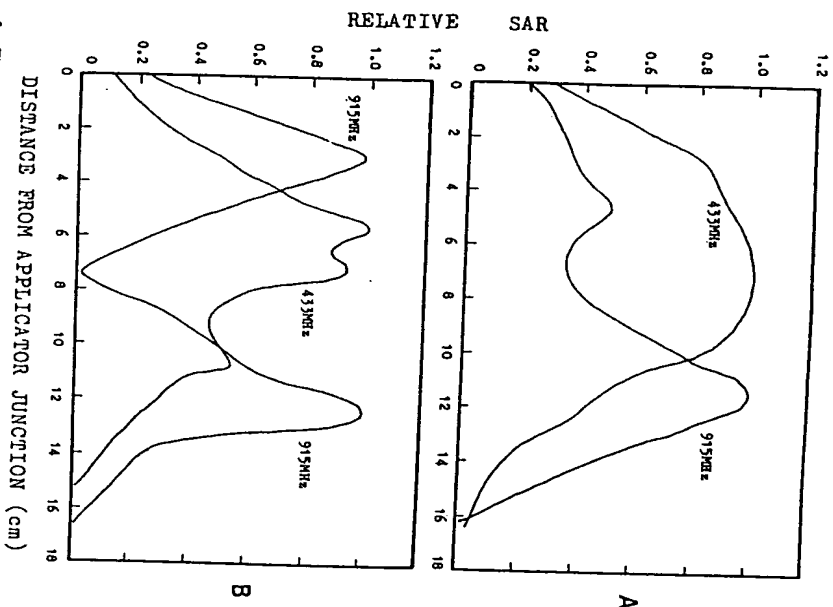
DISTANCE FROM APPLICATOR JUNCTION (cm)

Figure 5. The longitudinal relative SAR distributions along the surfaces of applicators: (A) was extracted from the results of Figures 2A and 3A. (B) was extracted from the results of Figures 4A and 4B. The SAR data were normalized to the surface maximum SAR values. The relations between relative SAR distributions and the active lengths of applicators are shown.

ssue. In addition, because the applicators are hand-made, it is difficult to cancel all r differences in their structure, so that the optimal operating frequency and impedance ing for each applicator may not always be the same. It is strongly suggested that ysical parameters be measured before each applicator is implemented clinically, and d have periodic quality assurance testing. Normally, it is sufficient to check it twice ear and preferably immediately before each use.

MIO applicators have small diameter, and touch the phantom or lesion directly. nwave fields decrease quickly with distance from the source in the near-field (Bassen Oakley 1982). so that heating volume is relatively small and frequency has no icant influence on penetration depth in the near-field. Hence there is no obvious

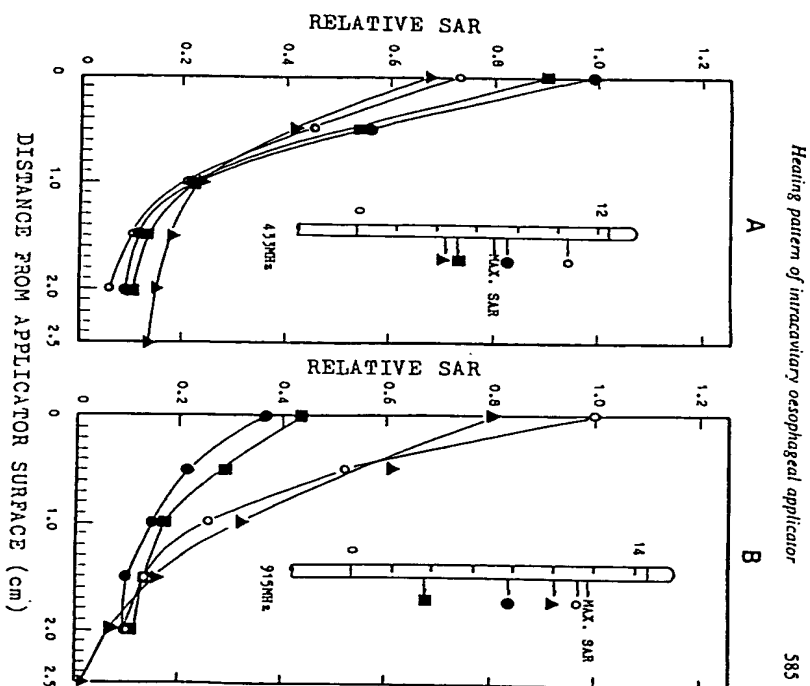DISTANCE FROM APPLICATOR SURFACE (cm)

Figure 6. (A) and (B) show the typical radial relative SAR distributions at several longitudinal positions for 433 MHz (Figure 2) and 915 MHz (Figure 3) applicators, respectively. The positions are indicated within this diagram. All SAR data have been normalized to its surface maximum SAR. ▲ Represents the results measured by fibreoptic thermometer, the other results came from thermograms.

difference between 433 MHz and 915 MHz applicators in RP50. The methods of increasing RP50 still need to be investigated. Adding local cooling may aid to increase RP50.

If reduced power is applied for a longer time the temperature distribution will change. becoming wider and more uniform, and the double heating regions for the 915 MHz applicator may not be seen due to thermal conduction. In this case the temperature distribution will no longer be representative of the power deposition pattern (Ccas 1982). Hence the burst of high power and short time were always used in our experiments.

In clinical application, usually lower microwave power (10-20 W) is used for a longer time (30-45 min). This may make temperature distribution in a small area more uniform, and this feature is useful in hyperthermia treatment. However, for those tumours that have good circulation of blood or large volumes, it is still difficult to make temperature rise evenly within the tumour with intracavitary hyperthermia only.